The New England
Journal of Medicine

Copyright, 1940, by the Massachusetts Medical Society

VOLUME 222 MAY 30, 1940 NUMBER 22

IMMUNITY TO VIRUS DISEASES*

Some Theoretical and Practical Considerations

ERNEST W. GOODPASTURE, M.D.†

NASHVILLE, TENNESSEE

ONE of the great difficulties encountered in the study of immunity from an experimental standpoint is the fact that, so far as medicine is concerned, there are few infectious diseases of man that can be induced in experimental animals with sufficient exactitude and constancy, amidst conditions simulating those under which they make their appearance naturally, to enable the investigator to translate his experimental data in terms of spontaneously occurring disease. This difficulty has tended to divert the attention of investigators away from studies of pathogenesis — that is, the mechanism of infection, without a knowledge of which specific immunity cannot be fully understood. Possibly it has been easier in the laboratory to follow and to measure the antibody response of an animal to the parenteral injection of various antigens than it has been to observe and to trace the progress and mechanism of spontaneous or induced infection. To understand the mechanisms of defense one should be able to watch the varying tide of battle between the active agent and the host, and to appreciate more intimately the tactics of the latter as it succeeds in gaining and maintaining the upper hand.

This perhaps can be more readily accomplished, at least to a certain extent, with viruses, because each of these agents affects a certain type or types of cells in a very specific way and often leaves cytologic traces of its progress.

Among the great basic facts of immunity are three that merit consideration: first, that there are relatively few types of microbial parasites that under ordinary conditions of life are capable of inducing infective disease, and each as a rule only in a limited number of varieties of hosts, the others being naturally immune; secondly, that the host is usually capable of offering active opposition to the advance and destructive influences of an established infection; and, finally, that after recovery the host is often, as a result of the experience of infection, much more resistant than before to a second infection by the same agent — that is, it acquires immunity. Except that every virus that is known is a pathogenic agent, the above facts are likewise the foundation of knowledge of immunity to viruses.

During the course of and following many infective diseases, changes take place in the circulating plasma of the host that are expressed by specific phenomena which make their appearance when the infectious agent or some of its products, or both, are brought into contact with the serum under appropriate conditions. These phenomena are agglutination, precipitation, lysis, complement fixation, toxin neutralization, opsonization and, in the case of serum from hosts that have overcome many kinds of virus infections, a specific inactivating effect on the corresponding virus when mixed with it under suitable in vitro conditions.

The potential importance to acquired immunity of antibodies that circulate in the body fluids is especially evident in the case of infections caused by micro-organisms that grow in and spread by way of the body fluids or produce injurious soluble antigenic products similarly distributed to the body tissues as a whole. The protective and curative effect, for example, of circulating antitoxin that combines with and neutralizes diphtheria toxin in vivo is apparent, and the beneficial influence on the course of pneumococcal pneumonia of type-specific antipneumococcus serum is explainable by virtue of the demonstration of the destructive effect of such a serum on the protective capsular polysaccharide that confers the antigenic specificity on each type and determines the production of an

*The Shattuck Lecture, delivered at the annual meeting of the Massachusetts Medical Society, Boston, May 21, 1940.

From the Department of Pathology, Vanderbilt University Medical School, Nashville, Tennessee.

†Professor of pathology, Vanderbilt University Medical School; pathologist-in-chief, Vanderbilt University Hospital, Nashville, Tennessee.

antibody peculiar to itself. Dissolution of the capsular material renders the pneumococcus a prey to phagocytosis by leukocytes in whose cytoplasm the denuded diplococci disintegrate.

But the toxin of the diphtheria bacillus and the capsule of the pneumococcus are surrounded by the body fluids because of the natural extracellular position of these antigens in the mechanism of their respective infections; and they are presumably immediately affected by their respective circulating antibody.

Matters become somewhat more complicated when we consider recovery from and active resistance to certain other infections, for example typhoid fever. In the blood serum of typhoid-immune animals and human beings there are bacteriolytic, bactericidal and agglutinating substances and, to a lesser extent, precipitating and opsonic bodies, but no true antitoxins.

Notwithstanding the rather detailed knowledge of antigenic constituents of the typhoid bacillus and of the numerous antibacterial effects elicitable from immune serum, it is admitted that from a theoretical standpoint the importance of specific antibodies in recovery and resistance is uncertain because the bacteria frequently disappear from the blood long before the patient is cured.

Furthermore, although one attack of typhoid fever protects against subsequent infection, circulating antibodies disappear from the blood of typhoid convalescents usually within the first seven months after recovery. The more durable immunity, therefore, cannot well be attributed to them, but rather to a greatly enhanced capability of response to small amounts of antigen on the part of the cells that have become accustomed, as a result of infection, to producing them rapidly and effectively.

Infection of man with the typhoid bacillus seems to entail a very complicated series of events, and until the background of pathogenesis of the disease is better understood one will probably not know just what protective mechanisms are involved and in what ways. The whole course of events in typhoid fever, a disease not yet reproduced in lower animals, is not explainable on the assumption of an extracellular parasite liberating antigens that are responded to by antibodies capable of acting directly on the exposed bacilli to destroy them immediately or to promote their destruction by cells. Dr. J. W. Adams and I[1, 2] have recently presented evidence that the typhoid bacillus in human infections may be at times in the course of the disease an intracellular parasite, nourished and supported in growth by the cytoplasm of plasma cells in intestinal and mesenteric lymphoid tissue. It would seem that so long as this intracellular reproductive phase of the infecting bacilli can be maintained, circulating antibodies should have little effect on them, and cessation of symptoms might ensue only after an undetermined break in this chain had taken place.

Intracellular infections by bacteria, protozoa and rickettsia introduce especial problems of their own, and they are possibly more closely related, as regards pathogenesis and immunity, to virus diseases than they are to extracellular infection, because the cell-parasite factor must be reckoned with in both instances.

The activity of viruses is as yet recognizable only by the changes induced in infected hosts, and all pertinent evidence indicates that these agents of disease require the internal medium of living cells for multiplication, whether they be inanimate molecules or obligate parasites. The hypothesis of cytotropism of viruses that formulates this doctrine is of great help in attempts to clarify and to render comprehensible the processes of pathogenesis, and to correlate them tentatively with the mechanisms of immunity.

Something of the cell-virus relation can be especially well demonstrated in fowlpox, a disease of birds that simulates variola in many ways; and its lesions may be correlated with the general pox group which includes not only smallpox, but alastrim, vaccinia and molluscum contagiosum. Fowlpox is an especially good example to illustrate the point at issue, because it is as yet the only virus disease in which the active agent has been proved experimentally to be inside infected cells and to be a constituent of a specific cellular inclusion such as one frequently finds in virus lesions. This experimental demonstration was made several years ago in collaboration with Dr. C. E. Woodruff.[3]

The wart-like lesions of fowlpox occur particularly in the skin, usually as a result of secondary localization of virus carried by the blood stream from a primary focus, probably most commonly situated in the mouth. The lesion is characterized mainly by hyperplasia and swelling of epithelial cells, each of which contains a relatively large intracytoplasmic mass known as the Bollinger body.

Dr. Woodruff and I found that trypsin in weakly alkaline solution rapidly freed the specific cellular inclusions of fowlpox from infected epithelial cells by dissolving the epithelial membrane and cytoplasm, so that the refractive inclusions, which are relatively quite large and substantial, could be obtained in quantity. By picking out individual inclusions with a micropipette and washing them in 2 per cent sodium chloride solution, until the washings no longer contained de-

monstrable active virus, we showed that a single washed inclusion inoculated into a feather follicle of a hen caused fowlpox infection at that site. Each well-formed inclusion contains many thousand minute particles, uniform in size, coccoid in shape, measuring 0.25 micron in diameter and possessing definite staining reactions. These are incorporated in the inclusions by a lipoproteid matrix, and they are known as the specific elementary bodies of this disease. By means of an attenuated glass point and microdissector, we were able to break up a single inclusion and to inoculate several feather follicles of a hen with minute fragments containing elementary bodies; the result was multiple infections with material from one inclusion.

This evidence indicates very strongly that the elementary bodies of the fowlpox intracellular inclusion are associated with the specific virus of this disease, and that they become agglomerated, together with a lipoproteid matrix, within the cell into a cytoplasmic mass, the Bollinger body. It has also been demonstrated that the elementary bodies of vaccinia and of molluscum contagiosum are intracellular and are the most important constituents of the respective cellular inclusions.[4, 5]

Further evidence that the elementary body of this and certain other virus diseases represents the virus particle itself is furnished by the facts that washed elementary bodies are infectious and that they are specifically agglutinable by immune serum.[6]

The peculiarity of virus infections as contrasted with most bacterial infections is this apparently necessary cell-virus relation that not only determines the characteristic picture of a particular disease but underlies the portal of entry and spread of virus, as well as its multiplication in the invaded host. It is that relation also which by determining the pattern of pathogenesis in any particular virus disease lends an especial fascination to its study. The intracellular position of the infectious agent, furthermore, may protect it from circulating antibody, and in other ways influence the mechanism of immunity.

A thorough understanding of the pathogenesis of particular virus diseases would involve a knowledge of such elements as portals of entry, primary infection, dissemination, secondary localization and elimination; and, if the hypothesis of cytotropism is to be of help, all these phenomena in the infectious process must be exactly related to the particular type or types of cell primarily invaded and those secondarily infected in each case, for complete immunity might be due in some cases to an acquired specific resistance limited to the type of cell at the portal of entry alone, other cells, such as those of the central nervous system, remaining susceptible. The cell-virus relation probably varies with every virus, and these variations may be spectacular, conferring complicated patterns of disease on the infected host. A few illustrations will, I hope, suffice to illustrate the principle involved.

There are certain viruses of human disease that seem to multiply within and to affect only the epithelial cells of the skin, for example those of warts and of molluscum contagiosum. The infectious agent is brought into direct contact with exposed susceptible epithelium from without, although in the case of warts, injury may result in secondary foci by lymphatic spread. Metastases do not seem to occur as a result of blood-borne virus. In the first example of infection it is quite likely that cutaneous injury exposes epithelium to contact with virus from the outside. These viruses are referred to as epitheliotropic, and are presumably obligately so. Because the lesions are confined to the skin and shed their component infected cells to the exterior, it is possible that relatively little antigenic material gains entrance into the body, and these diseases tend to run a rather long course.

There are other virus diseases of man that are characterized clinically by a cutaneous eruption, and in the skin lesions, epithelial cells are likewise prominently involved. Examples of such diseases are smallpox, chickenpox and possibly measles. In the lesions of these diseases, certainly in those of variola and varicella, virus affects not only epithelial cells but also those of mesodermal origin, such as fibroblasts and endothelium. This is of importance with reference to spread and secondary localization of these infections, which evidently take place by way of the blood stream. A primary lesion occurs no doubt somewhere in the upper respiratory tract; thence virus liberated from infected cells gains entrance into the blood stream to relocate in the skin and internal organs, where there are accessible susceptible cells, to form secondary foci.

In a third group of virus diseases of man the nervous system is especially involved. Of this group the viruses of poliomyelitis and rabies seemingly are obligately neurotropic; that is, they appear to require the medium of neurones for their multiplication and spread.

The conception of cytotropism is of fundamental significance to an interpretation of the pathogenesis of such various types of infection, for, if it be true, then the portal of entry of each obligate neurotropic virus must be through neural channels. In the monkey, at least, this appears to be

the case with the virus of poliomyelitis, because following intranasal instillation the pathway of infection seems to be along the exposed filaments of the olfactory mucosa, thence by way of axones and dendrites to the olfactory bulb, thence to the brain and spinal cord. Similarly the bite of a rabid dog introduces rabies virus from the saliva into injured tissue containing exposed nerve processes, and it appears that it is through these endings and axones that the virus reaches the central nervous system, to disseminate there likewise through neural channels. Experimental evidence for neuronal spread has been obtained especially from studies of herpetic infection in rabbits.[7]

Other viruses that affect the nervous system are not so restricted in their requirements, but affect more than one type of cell. Among these are the viruses of St. Louis encephalitis, equine encephalomyelitis and yellow fever; in lower animals a good example of this group is the virus of canine distemper. Such viruses as these probably enter the brain to infect neurones or supporting tissue only by way of the blood stream, and the portal of entry might be a cutaneous injury, such as the bite of a mosquito, that exposes capillary endothelium and blood to the virus.

The viruses that affect more than one type of cell, such as those last named, have been referred to as polycytotropic viruses, and I regard this term as more appropriate than pantropic or viscerotropic, although the latter are often employed. The use of the term polycytotropic, however, does not obviate the necessity of demonstrating each kind of susceptible cell in every case, because from the standpoint of understanding these infections, their pathogenesis and eventually the mechanism of immunity to them, it is of great importance to know just what specific types of cell are affected and how cytotropism determines pathogenesis. DeMonbreun's[8] studies of canine distemper show that not only epithelial cells but also vascular endothelium is susceptible to this virus. Infection of vascular endothelium is no doubt concerned with spread of the virus; and localization of the infection in the brain is probably not through neurones but by way of the vascular endothelium as the portal of entry from the blood stream. It is possible also that a similar mechanism exists in St. Louis encephalitis and equine encephalomyelitis. In yellow fever it might also be that endothelium is first infected, and that virus thence liberated into the blood stream localizes secondarily in the cells of the liver.

No virus has yet been cultivated in the absence of living susceptible cells, and because of this fact it is a difficult matter to obtain viruses in a state of purity and in quantity necessary for extensive analyses. Their nature remains undetermined, but they appear to lie somewhere along the borderland of the living and the inanimate, possibly constituting a liaison between them. They are particles of different size, they contain nucleoprotein, and they are antigenic. Frequently recovery from infection is followed by specific resistance to reinfection that lasts for varying periods, from weeks to many years, and occasionally perhaps throughout life, depending largely on the type of virus. The striking immunity so often observed makes the virus infections especially interesting from the standpoint of acquired resistance, and has led to the practices of prophylactic immunization by passive transfer of specific serum or vaccination with modified active virus and even with noninfective preparations, which in some cases have proved to be effective.

As in bacterial infections, specific antibodies also appear in the serum of animals that have recovered from virus diseases or have been actively immunized by vaccination. The virus antibodies simulate in general those demonstrable as a result of infection or vaccination with bacteria, but it is to be especially emphasized that virus infection elicits the production of specific antibodies that, under proper conditions in vitro, have a neutralizing effect on the virus concerned, and that this reaction simulates the toxin-antitoxin reaction. In regard to immunity it is possible that the effect of this antiviral antibody at least in some cases is in relation to the cell-virus complex, as it might operate to prevent virus from entering susceptible cells.

But one must be cautious in such interpretations, and I wish to emphasize that the phenomena of active resistance to recurrence of a specific virus infection are not necessarily coexistent with the presence of these demonstrable changes in the serum. The occurrence of specific antibodies in the blood serum of recovered hosts does not always signify immunity, nor is there as yet a well-established relation of specific antibodies to the state of heightened resistance or immunity that follows natural virus infection. It has been shown, for example, in the case of vaccinia virus that a rabbit vaccinated with inactive elementary bodies to the extent that its blood serum contains abundant agglutinating, precipitating and complement-fixing antibodies is just as susceptible to infection with active vaccinia virus as is a normal rabbit.[9] It would seem more likely that the antibody that neutralizes a virus in vitro is related in some way more directly to the mechanism of immunity than are those responsible for agglutination and precipitation; yet such experiments as those of Hodes and Webster[10] with the virus of the St. Louis type of encephalitis

make it appear very doubtful that, in this infection at least, there is any such relation. These investigators showed that mice vaccinated with the St. Louis encephalitis virus become highly immune and continue so for six weeks after vaccination, at which time few or no neutralizing antibodies are demonstrable in their serums. Then immunity begins to wane, and as it lessens, neutralizing antibodies make their appearance and rapidly increase in amount, to reach their height twenty-two to twenty-four weeks after vaccination, at a time when the animals have ceased to be resistant to reinfection.

No toxins have been demonstrated in virus lesions, and consequently no evidence of antitoxins in immune serums has been found. Little is known about phagocytosis of viruses as a combative mechanism, or about the participation of complement in any destructive capacity.

It is obvious, therefore, that the mechanisms involved in immunity to virus infections are not at present clearly understood, and they are unlikely to be until a better comprehension of their relation to pathogenesis of these infections has been attained.

Notwithstanding the inability to explain the mechanism of immunity on the basis of known specific humoral antibodies, the rather anomalous situation exists that, in the case of at least a few viruses, infection can be prevented by a properly timed and measured dose of specific antiserum. This is an established prophylactic practice for the prevention of measles — presumably a virus disease. A similar practice seems to be of preventive effect against mumps, and experimentally it is effective to some extent against others, including vaccinia. These are empirical facts, however, and they do not elucidate the mechanism of heightened resistance. The explanation will no doubt eventually be found in additional knowledge concerning pathogenesis, which is determined by the cell-virus relation.

Some students of virus diseases think that the formerly susceptible cells of a recovered host acquire a specific resistance as a result of virus infection, and that such a change is of equal or even greater importance in some cases than is the acquisition of humoral antibodies. But the assumption of acquired cellular immunity separate and apart from humoral antibodies has not been well substantiated by direct experiment.

I should like in this connection to refer briefly to some studies we[11] have made with the virus of fowlpox previously mentioned. These experiments were undertaken to determine whether or not we could find evidence of an increased cellular resistance to infection in fowls with acquired immunity. This disease offered, we thought, an exceptionally favorable opportunity for experimental study of certain phases of this problem because the virus affects especially cutaneous epithelium, manifesting itself by easily recognizable specific cellular inclusions, and because the skin can readily be grafted onto the chorioallantois of chick embryos from both normal and immune fowls. The latter fact affords a favorable method for studying the behavior of cutaneous epithelium under different environmental circumstances.

Our first objective was to determine whether or not established skin grafts from normal and immune fowls were susceptible to infection with the virus of fowlpox, as manifested by the development of the pathognomonic Bollinger bodies within the cytoplasm of the epithelial cells following inoculation.

These experiments conclusively proved that the epithelial cells of skin from chickens with an acquired immunity to fowlpox and completely resistant to infection by cutaneous inoculation, while a part of the immunized host, become quite as susceptible to infection by this virus as do grafts of normal skin after grafting onto the chorioallantoic membrane. If such grafts, as well as those from normal chickens, were regrafted onto muscle of immune chickens and inoculated, no infection took place. Normal skin, on the other hand, if regrafted onto the muscle of normal chickens, was quite susceptible to infection by inoculation. We found no indication, therefore, of the existence of an acquired immunity inherent in the epithelial cells themselves, but our results pointed rather to humoral or local factors in other tissues as the cause of acquired resistance of the normally susceptible epithelium.

Under some circumstances acquired insusceptibility of certain cells of a host seems out of proportion to the concentration of demonstrable circulating antibody, and this is the case with epithelium of chickens immunized to fowlpox. One is tempted to conjecture that humoral antibody might be concentrated in the skin, perhaps inside the epithelial cells themselves, from the surrounding medium. When grafted onto the chorioallantois such antibodies would become diluted by the plasmatic circulation in the graft and thereby be rendered ineffective. There is little experimental basis for such an assumption, although the reported success of McKinley[12] and of Hallauer[13] in conferring passive immunity to rabbits against intracerebral injection of herpes virus by repeated doses of immune serum, while no cerebral immunity could be demonstrated after a single large

dose, might be interpreted to mean that after a period of time circulating antibody kept at a high level by repeated administration might finally penetrate the cerebrospinal fluid or the nerve cells themselves, temporarily heightening their resistance.

So far as our own investigations have enlightened us, immunity to those virus infections with which we have worked, especially fowlpox and herpes simplex, appears to be importantly contributed to by something of a specific nature circulating in the blood. What this something is and how it works to prevent or ameliorate infection we do not know. We should suppose it to be a specific antibody, but whether it is one of those demonstrable by in vitro tests or another as yet unrecognized is obscure. This hypothetical antibody to fowlpox does not necessarily operate in such a way as to prevent virus from entering susceptible cells and inducing typical lesions, as was shown by the following recent experiment.

After a certain dose of hyperimmune hen's serum was injected intravenously into baby chicks, the down of whose heads had been plucked, and this was followed by an intravenous dose of fowlpox elementary-body suspension, just as many lesions developed in the injured skin, eyelids, mouth and stomach as appeared in controls treated the same way except that they received normal hen's serum. However, the controls rapidly became sick and died several days earlier than did those passively immunized. Some of the latter recovered after the lesions, which continued to increase in size for a while, aborted and healed prematurely. These experiments are not yet complete, but it seems at present that the immune serum might act, among other ways, to protect the chick against some injurious agent elaborated as a result of infection rather than to prevent the infection itself, although it certainly exerts an inhibiting effect on the full development of established lesions.

One is hardly in a position at present to exclude some active participation at times of the susceptible cells themselves in the immunity process, because actual infection of a given type of cell, for example the cerebral neurones of a rabbit with herpetic encephalitis, confers after recovery a strong immunity to subsequent intracerebral injection of herpetic virus that seems to be independent of circulating antibody, while keratitis alone, although it confers immunity to subsequent corneal inoculation and stimulates the formation of antibody, often does not protect the brain from infection by intracerebral inoculation.

It is possible that it is necessary for active virus to enter susceptible cells in order that they may respond in some way to heighten their resistance, for example by the local formation of antibody. If this should be true it might explain the frequent failure to induce effective resistance by the injection of inactive vaccines. Active virus evidently has the capacity to enter susceptible cells, but if the virus becomes altered in such a way that it does not induce infection, that alteration might also be of such a nature as to destroy its capacity to gain entrance into cells ordinarily susceptible, and thus to elicit a protective response to it. But on this hypothesis one must assume that virus enters all susceptible cells, and there is no evidence of this at present. On the other hand, circulating antibodies might enter and to a certain extent become concentrated in the course of time in cells that do not produce them. Passive immunization of the brain of rabbits against an intracerebral injection of herpes virus by repeated injections of immune serum might be explained in this way, for a single large dose of immune serum is not protective.

There is one group of virus diseases that should be especially susceptible of modification or prevention by parenteral injection of immune serum; that is the group in which the virus is spread in early stages of the disease by the blood stream, particularly if endothelium is infected. In this group one might tentatively include yellow fever, variola, varicella and measles. One can reasonably assume an initial lesion from which virus is thrown into the blood stream, or an initial infection of vascular endothelium itself such as can be induced experimentally in canine distemper and in experimental herpetic infection of the chick embryo, which will be described later. If circulating antibody be present during the development of the primary lesion, blood dissemination and metastasis may be prevented or modified provided virus is exposed to antibody in the circulating fluid. In all likelihood this is the way in which an early administered dose of measles-immune serum exerts its protective effect.

In another group of virus diseases, including especially those in which the virus seems to be obligately related to nerve cells, such as poliomyelitis and rabies, there would seem to be much less likelihood of favorably influencing the course of the infection by the introduction of immune serum, because virus can gain access to and spread through the nervous system by means of neural processes, apparently without becoming subject to the influence of circulating inhibiting factors. Indeed, the use of immune serum in these diseases has been of no evident avail. Repeated injections of immune serum for several weeks before infection has taken place might, however, confer protective passive

immunity for a short while, in view of Hallauer's[13] experiments with herpes simplex.

In the first group of diseases in which virus is blood-borne, the chances of effective immunization by a proper inactive vaccine would seem to be far superior to those obtaining in the second group, in which antibodies actively or passively acquired circulate but do not presumably come into contact with intracellular virus.

The interrelation of pathogenesis of a virus infection and immunity cannot, I think, be illustrated better than by reference to clinical pictures and experimental infections caused by the virus of the cold sore or fever blister. Herpes simplex infection in human beings has several rather distinct and characteristic clinical manifestations, and it is quite likely that each is due to the particular balance existing at the time between susceptibility and immunity of the host and to the peculiar intimacy that obtains between the virus and certain types of cell.

The common type of herpes in adults is the ordinary labial variety, but rather recently Drs. K. Dodd, L. M. Johnston and G. J. Buddingh,[14] at Vanderbilt University Medical School, have identified herpes simplex virus as the specific etiologic agent of a stomatitis of infants and children that heretofore has probably been included in an indefinite group of diseases to which pediatricians have given the name "aphthous stomatitis." These investigators consider herpetic stomatitis, which is sometimes accompanied by rather severe general symptoms, as representing a primary infection. This point of view is maintained also by Burnet and Lush,[15] who confirmed the previous work, and found further that children who had herpetic stomatitis possessed no virus-neutralizing antibody in their bloods. Following recovery, however, antibody was present.

It would appear that subsequent attacks of herpes, occurring most commonly in adult life, take place in individuals whose blood serums already contain antibody signifying previous infection, and that these people show no herpetic virus in their saliva during or between attacks. The presence, therefore, of antiviral antibody in the blood is not preventive of herpetic infection of the lip but, probably owing to previous infection, indicated by the presence of antibody, the clinical manifestation is different in that the intraoral mucosa escapes.

In a third type of herpetic infection the eruption breaks out repeatedly in the same area of skin, and sometimes in definite relation to a particular cutaneous nerve. In these cases, neutralizing antibody is also present in the blood.

It is an interesting adventure in speculation to try to interpret such varied phenomena in terms of known fact and acceptable current hypothesis. It seems evident in the first place that circulating neutralizing antibody, in such concentration at least as exists under the circumstances, is ordinarily not sufficient to protect epithelial cells of the lip from infection with herpes virus from the outside. In those cases where the cutaneous eruption is definitely related to a particular nerve there is more difficulty in explaining the phenomenon of infection, and at the present time it seems most logical to conclude that the virus remains latent within nerve cells over long periods, manifesting itself by infecting epithelial cells when unknown conditions arise to permit restoration of its activity. This is possibly true also in the case of the usual labial herpes, for in many cases there is no evidence of contact with extraneous virus. If the assumption of latent herpetic infection of nerve cells be accepted, then one must reckon with a complex and variable intracellular immunity mechanism, concerning the nature of which there is no knowledge.

It may be concluded from the observed facts that, ordinarily at least, cutaneous epithelium in itself does not possess innate immunity in those subject to herpes, but that a change resulting from an initial infection, indicated by a virus-neutralizing effect of serum, alters the clinical picture and course of subsequent infections.

Herpetic virus is very infectious for the rabbit, and much knowledge of the host-virus relation has been derived from experimental infections in this animal. Inoculated on the cornea the virus infects the epithelial cells, inducing an acute keratitis. With many strains of virus the infection does not stop at the eye but proceeds rapidly to the brain, following the course of fibers of the sensory division of the fifth cranial nerve and utilizing the medium of the axis cylinders as pathways for its invasive progress. Frequently the encephalitis is fatal. The blood stream is not at all or rarely invaded. Should an animal recover from its encephalitis it is immune to reinfection, even by intracerebral injection of many lethal doses for normal rabbits; and because little or no circulating antibody may be demonstrable there is some reason for the belief that a specific resistance has taken place in the neurones themselves.

Miss Katherine Anderson,[16] at Vanderbilt, has recently observed, in her studies of herpetic infection of chick embryos, the sudden appearance of a variant of the virulent HF neurotropic strain of herpes virus (Rockefeller Institute), which has become so altered by chick embryo passage that it

causes only a mild acute keratitis in inoculated rabbits; the infection stops at the cornea, and there is no invasion of the brain. These rabbits become immune to reinoculation of the cornea with the virulent HF strain, and neither keratitis nor encephalitis may follow a heavy inoculation, but the brain may remain susceptible to infection if virus is injected intracerebrally. Here, then, is a case in which as a result of the experience of a previous peripheral infection the host has become resistant at the portal of entry, while remaining susceptible to virus that might break through to reach the nervous system. Protection of a natural portal of entry, however, would be adequate no doubt in the ordinary course of events to prevent disease, and the modified herpes strain represents a desirable type of variant for prophylactic inoculation.

In human infection with herpes virus and in that induced in rabbits there is no evidence of blood-borne metastasis. Recovery from infection, however, may be associated with the appearance of antiviral antibodies in the blood stream. The presence of such antibodies is not incompatible with susceptibility to reinfection, although the resulting disease might be different from the primary infection, at least in man.

In connection with the pathogenesis of this infection and with reference to immunity, the recent success of Miss Anderson[17] in inducing blood-borne metastases in chick embryos is of great interest. She has been able to adapt a strain of herpes virus, by repeated membranal cultures, to the tissues of chick embryos. By passage in this host the virus has become modified in such a way that its virulence for the embryo has become greatly enhanced, and its capacity to infect cells of mesodermal origin, especially endothelium, has become augmented. As a result of this change, inoculation of the chorioallantoic membrane results not only in a local infection of that structure, but also in an extension by continuity and hematogenous metastasis to a number of internal organs, especially the liver, heart, spleen and kidneys. The mechanism of hematogenous dissemination seems to depend on the enhanced ability of the virus to infect the endothelial cells of blood-vessel channels, thus initiating foci of infection that spread to cells of the parenchyma. Hematogenous spread by endothelial infection has not, I believe, been previously observed in herpetic infection of other animals, and Miss Anderson's experiments introduce a new element into the problem of pathogenesis of this interesting experimental disease.

Because extension of the infection from the membrane to internal organs appeared to be by way of vascular endothelium, an opportunity was presented to observe the effect of passive immunization by means of intravenous injection of hyperimmune hen serum on the course of the experimental disease; and Miss Anderson was able to show quite clearly that intravenous introduction of such an immune serum not only inhibited or prevented blood-borne metastasis, but likewise modified the local lesion and prolonged the life of the embryo.

Thus it has been shown experimentally that the presence of circulating immune bodies may not prevent a local herpetic infection of the skin or brain, but that passively conferred humoral antibodies may prevent spread of the infection by way of the blood stream if that spread is associated with infection of vascular endothelium.

If one accepts the possibility of latent herpetic infection of human neurones or other cells, it must be assumed that resistance to virus activity during inter-eruptive periods is dependent on a rather delicate and variable intracellular chemical or physical balance of a temporary nature and probably not dependent on antibody, because a great variety of conditions, such as hyperthermia and proteid and chemical intoxications, are readily followed by evidences of reactivated pathogenicity, as manifested by an eruption of labial herpes. The idea of lability of cells in respect to their susceptibility and resistance to viruses seems to be a rather hopeful conception, because it points to the possibility of modifying cells intentionally in the direction of increased resistance by chemical or other means.

Different methods are being used at the present time with varying degrees of effectiveness to control or modify virus diseases. These methods have already been mentioned, namely active immunization by infection with a mild virus, active immunization by injection of inactive virus material and passive immunization by the injection of immune serum.

Active immunization by infection with a mild virus started with Jenner, and has been successfully employed ever since in the prevention of smallpox. In the last few years the same principle has been employed in the prevention of yellow fever and of certain virus diseases of animals. The outlook for this method is very hopeful, for strains of viruses are readily variable, and it has been possible to modify some of them experimentally so that they may be more safely used as active vaccines.

Active immunization for protection against yellow fever was made possible by the work of Theiler,[18] at the Harvard Medical School, which showed that this virus can be modified in its virulence and pathogenicity by passage through the

brains of mice. Thus changed, the virus no longer induced yellow fever when injected subcutaneously into susceptible monkeys. This modified, so-called "neurotropic" yellow fever virus has been used for human vaccination, but another strain has been employed on a larger scale and probably with less hazard after modification by repeated tissue culture.

Immunization with an active virus is most effective if actual infection is induced, but the induced disease must be mild and without important hazard if it is to be successfully applied in human prophylaxis. In some cases the use of an active virus so attenuated that it does not induce infection might be superior to an inactive product, because of better antigenic properties. This can be accomplished with some viruses by introducing them into tissues whose cells are not naturally susceptible. Pasteur, for example, finished his vaccinations for rabies with active virus in emulsions of rabbit cord injected subcutaneously, preceded by several injections of inactive material. It would, of course, be an unsafe procedure in any case to attempt human immunization with an infecting dose of virulent virus.

Injection of specific immune serum at a proper time will prevent or modify measles, and immunization with inactive vaccines has been used to protect against rabies, with, at least in the dog, uncertain success. Inactive preparations of the virus of equine encephalomyelitis cultivated in the chick embryo appear to be quite satisfactory in protecting horses and perhaps man. Antiviral antibodies appear in the serum of vaccinated animals following injections of the inactive vaccines in each of these cases, but in view of the circulation of virus in blood and the susceptibility of cells presumably of mesodermal origin in the case of equine encephalomyelitis, it is perhaps simpler to attribute protection against that disease to the presence of such antibodies — an assumption which is more questionable in the case of induced immunity to rabies, where the virus in the usual course of events does not necessarily contact circulating antibody.

Protection by vaccination with apparently inactive material against such a virus as rabies has raised the question in many minds as to whether the vaccines that do protect are entirely free of active virus, although the infection be inapparent. Unfortunately there is no way to be absolutely sure about this at present.

There is still hope, however, of inducing variations in obligate neurotropic viruses, — such as those of rabies and poliomyelitis, — similar to those already found in the case of the virus of smallpox and of yellow fever, that will induce without hazard a mild infection followed by immunity. In this connection I should like to mention briefly some recent experiments of Dr. James R. Dawson, Jr.,[19] at Vanderbilt, with the virus of rabies.

Dr. Dawson has succeeded in infecting the brains of chick embryos with several strains of rabies virus, including a street virus, a fixed virus and a strain derived from human infection. After being passed through several generations by successive intracerebral inoculations of chick embryos with infected brain, the street virus was injected by the intracerebral route into rabbits. All of 19 rabbits thus inoculated developed acute encephalitis with fever and a peculiar weakness and incoordination of the muscles, especially those of the neck. Thirteen of the 19 recovered, and 4 of these selected at random were completely immune to a heavy intracerebral dose of street virus, while 2 controls that received one hundredth as much rapidly succumbed with rabies.

This, I believe, is the first time a strain of rabies virus has been so modified that it would induce an immunizing and self-limited acute encephalitis in any animal species. A similar alteration of virulence for the dog would very likely be of great practical importance in the control of this distressing disease, but the strain so altered in virulence for rabbits is still fatal for dogs, at least in large doses, although Dr. Dawson is hopeful of inducing further modification that will be of help.

In conclusion, I should like to reiterate my main thesis that a knowledge of pathogenesis of virus diseases is necessary to a complete understanding of immunity. The patterns of pathogenesis of these diseases are determined by the cell-virus relation, which depends on the requirement by the virus of the internal medium of living susceptible cells for multiplication. The portal of entry, the primary lesion and the dissemination and elimination of each virus depend on the accessibility of certain susceptible cells in each case.

Although the mechanism of immunity is not yet well understood, experimental investigations indicate that, in at least most cases, humoral antibodies are very important factors, although their presence does not always indicate immunity or explain its phenomena. It has not yet been proved that susceptible cells themselves can actively participate in creating the resistant state, although their role is not known. Immunity does not depend entirely on a state that prevents virus from entering susceptible cells. Immunity is relative, and with certain infections of man partial immunity will modify the clinical features of the disease.

REFERENCES

1. Goodpasture, E. W.: Concerning the pathogenesis of typhoid fever. *Am. J. Path.* **13**:175-186, 1937.
2. Adams, J. W., Jr.: Intracellular bacilli in intestinal and mesenteric lesions of typhoid fever. *Am. J. Path.* **15**:561-566, 1939.
3. Woodruff, C. E., and Goodpasture, E. W.: The infectivity of isolated inclusion bodies of fowl-pox. *Am. J. Path.* **5**:1-9, 1929. Relation of virus of fowl-pox to specific cellular inclusions of the disease. *Ibid.* **6**:713-720, 1930.
4. Goodpasture, E. W.; Woodruff, A. M., and Buddingh, G. J.: Vaccinal infection of the chorio-allantoic membrane of the chick embryo. *Am. J. Path.* **8**:271-280, 1932.
5. Goodpasture, E. W., and Woodruff, C. E.: A comparison of the inclusion bodies of fowl-pox and molluscum contagiosum. *Am. J. Path.* **7**:1-8, 1931.
6. Goodpasture, E. W.: Vaccinia (Ludvig Hektoen Lecture). *Proc. Inst. Med. Chicago* **11**:206-220, 1937.
7. *Idem:* Herpetic infection, with especial reference to involvement of the nervous system. *Medicine* **8**:223-243, 1929.
8. DeMonbreun, W. A.: The histopathology of natural and experimental canine distemper. *Am. J. Path.* **13**:187-212, 1937.
9. Parker, R. F.: Immunological studies of a heat-stable substance isolated from tissues infected with vaccine virus. *J. Exper. Med.* **67**:361-367, 1938.
10. Hodes, H. L., and Webster, L. T.: Relation between degree of immunity of mice following vaccination with St. Louis encephalitis virus and the titre of the protective antibodies of the serum. *J. Exper. Med.* **68**:263-271, 1938.
11. Goodpasture, E. W.; Douglas, B., and Anderson, K.: A study of human skin grafted upon the chorio-allantois of chick embryos. *J. Exper. Med.* **68**:891-904, 1938.
12. McKinley, E. B., and Holden, M.: Immunologic studies in experimental encephalitis. *Arch. Path. & Lab. Med.* **4**:155-161, 1927.
13. Hallauer, C.: Ueber die passive Immunisierung des Zentralnervensystems gegenüber Herpes- und Hühnerpestvirus. *Ztschr. f. Hyg. u. Infektionskr.* **119**:505-512, 1937.
14. Dodd, K.; Johnston, L. M., and Buddingh, G. J.: Herpetic stomatitis. *J. Pediat.* **12**:95-102, 1938.
15. Burnet, F. M., and Lush, D.: Herpes simplex: studies on the antibody content of human sera. *Lancet* **1**:629-631, 1939.
16. Anderson, K.: The encephalitogenic property of herpes virus. *Science* **90**:497, 1939.
17. *Idem:* Pathogenesis of herpes simplex virus infection in chick embryos. *Am. J. Path.* **16**:137-155, 1940.
18. Theiler, M.: Studies on the action of yellow fever virus in mice. *Ann. Trop. Med.* **24**:249-272, 1930.
19. Dawson, J. R., Jr.: Infection of chicks and chick embryos with rabies. *Science* **89**:300, 1939. Also personal communication.

HYDRONEPHROSIS: STANDARDIZATION OF SURGICAL TREATMENT*

THOMAS E. GIBSON, M.D.

SAN FRANCISCO, CALIFORNIA

REFERENCE to the voluminous literature on hydronephrosis reveals a renewed interest in the last decade in the problem of ureteropelvic obstruction and its surgical correction. The historical aspect of this problem has been reviewed in detail by Mathe.[1] Trendelenburg[2] is given credit for the first attempt at plastic repair in 1886, but his effort proved unsuccessful owing to death of the patient from intestinal obstruction. In 1891 Küster[3] reported the first successful plastic operation on the renal pelvis. His operation consisted in reimplantation of the excised ureter in the pelvis at its most dependent part. One year later, Fenger[4] described a plastic operative procedure that he had done for the relief of hydronephrosis due to valve formation and stricture of the ureter. This consisted in longitudinal incision at the point of obstruction, with transverse closure, an adaptation of the Heineke-Mikulicz principle used in intestinal surgery. Study of the many types of plastic procedures subsequently applied to the correction of ureteropelvic obstruction shows a fairly close parallelism to methods that have become more or less standard in gastrointestinal surgery. The stimulus of this early work led to an era in which the renal pelvis became the recipient of surgical attention that was perhaps more enthusiastic than discriminating. There were many failures, and even those cases in which the results were termed successful must be accepted with reservation, since they antedated the development of urography with its present-day precision in the evaluation of surgical end results. Even at the present day, no one is justified in citing an end result as successful without the evidence of urography after a sufficient postoperative period has elapsed. Silent destruction of the kidney may occur postoperatively and give a false impression of cure unless checked by careful urological investigation.

That the earlier enthusiasm for conservative plastic surgery waned or fell into disfavor is evident from a review of the discussion of hydronephrosis that occurred at the German Urological Congress in Vienna in 1921, where the fact was disclosed that up to that time nephrectomy was the generally accepted operation for hydronephrosis. Since then there has been a gradual recrudescence of interest in conservative plastic surgery, which received a real impetus in the symposium on hydronephrosis participated in by Von Lichtenberg, Walters, Quinby and others at the annual meeting of the American Medical Association in 1929. Reference to the symposium on hydronephrosis of the American Urological Association at Minneapolis in 1937 furnishes a good cross-section of the progress that has been made in the last decade, and other noteworthy contributions in the last few years have served to establish the plastic surgery of ureteropelvic obstructions on a firm foundation.

However, in spite of this progress it is still the common practice to perform nephrectomy on many

*Read at a meeting of the New England Branch of the American Urological Association, Boston, February 15, 1940.

hydronephrotic kidneys that might have been saved by plastic surgery. Reasons for this unfortunate state of affairs, as enumerated by Ormond,[5] are unfamiliarity on the part of the profession with the methods that can be employed, lack of confidence in plastic operations as a remedy for hydronephrosis, and lack of agreement as to the preferable type of operation and lack of standardization of procedure.

In the surgical correction of ureteropelvic obstruction, four basic methods have been oftenest used (Fig. 1). These are as follows: reimplantation of the excised ureter in the pelvis at its most dependent part (Küster); longitudinal incision, with transverse closure (Fenger); the Y incision with the V closure (Schwyzer, Foley); and some type of lateral anastomosis, either with the pelvis or another portion of the ureter (Trendelenburg, Priestley).

The fourth type of repair is essentially the original Trendelenburg operation, and is similar to the Finney pyloroplasty. Von Lichtenberg's operation is a variation of the same fundamental principle. In the presence of a vascular band containing an artery too large to sacrifice with safety, Young's[6] plastic procedure may occasionally be applicable, although most surgeons have surmounted this problem by the first method enumerated above. Figure 2 shows my modification of the Fenger operation.

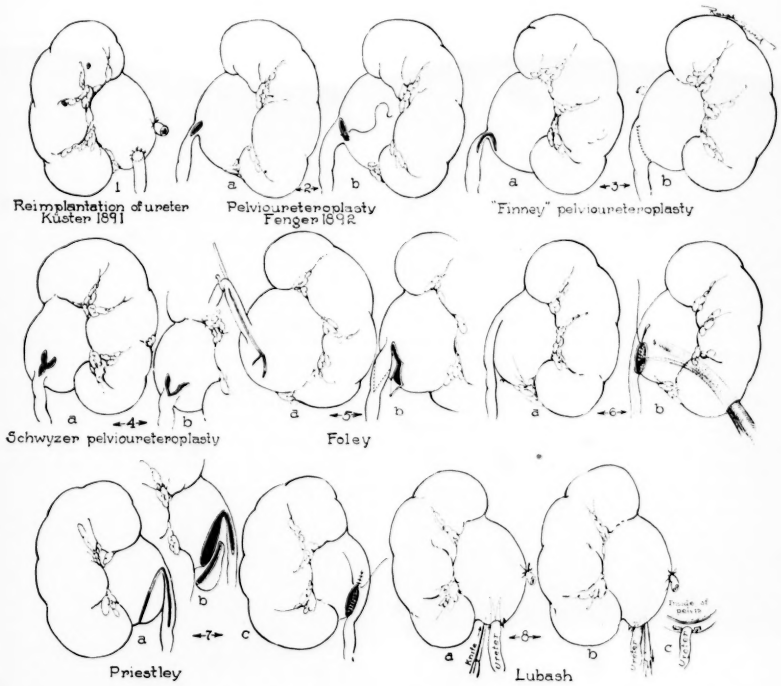


FIGURE 1. *Sketches Illustrating the Main Types of Pyeloureteroplasty Now in Vogue.*

A study of the literature reveals that no one of the methods used in the past has been an unqualified success. Statistical reviews of end results of plastic operations in the more recent series reported indicate failure in anywhere from 15 to 33 per cent of cases.

Reasons for failure are enumerated by Lubash[7] as follows: leakage of urine and perirenal infection at the point of anastomosis; tension along the suture line, with secondary infection; puckering

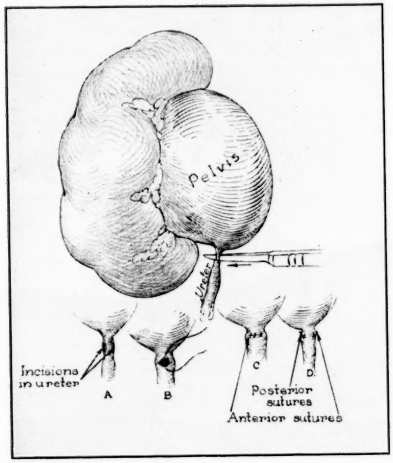


FIGURE 2. *Drawing Illustrating the Author's Modification of the Fenger Operation.*

A Bard–Parker No. 11 blade is used to transfix the strictured area at the ureteropelvic junction. This might be termed a double Fenger operation. It is suited to Type I hydronephrosis, but as a rule the Rammstedt procedure is preferred because of its simplicity, and the facts that incision is not made into the lumen of the ureter and that no suturing is necessary.

and buckling at the line of anastomosis; new stricture formation, acting as a boomerang; retention of urine and secondary pyelonephritis or cortical abscess formation; and persistent urinary fistula.

It is evident that the present methods of surgical treatment of hydronephrosis leave much to be desired, and it is therefore appropriate at this time to take an active interest in the problem of saving hydronephrotic kidneys from nephrectomy or ultimate destruction through unsuccessful plastic surgery. I believe that there are still more fundamental reasons for failure which have not previously been sufficiently stressed, and that more uniform success will follow the adherence to two simple types of surgical procedure adapted to the two main types of hydronephrosis.

Obstructions at the ureteropelvic outlet fall naturally into two main groups (Fig. 3): Type I, stricture of the ureteropelvic junction; and Type II, valve formation caused by high insertion of the ureter into the pelvis.

Both types are frequently complicated by extrinsic factors such as compression or kinking at the ureteropelvic juncture caused by bands, either fibrous or vascular, by ptosis or by adhesions, either inflammatory or congenital. Figures 4 to 9 show the successive steps of the two operations which in my experience are best adapted to these two types of hydronephrosis. The first necessity is, of course, the removal of all obstructing bands and adhesions; in other words, a thorough pyelo-

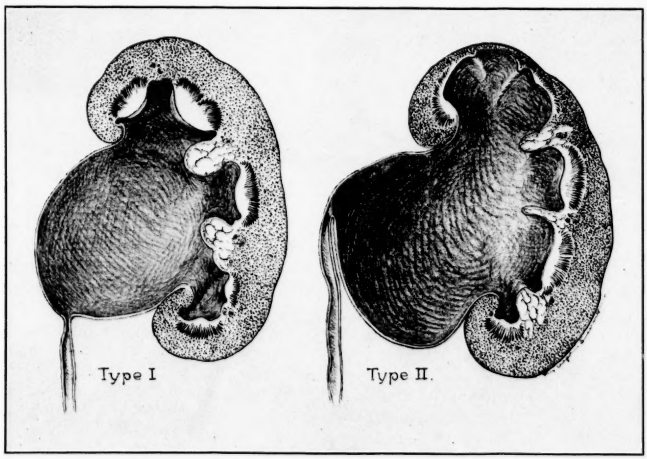


FIGURE 3. *Drawings Illustrating the Two Main Groups into Which All Cases of Hydronephrosis Fall.*

Type I—stricture of the ureteropelvic juncture.
Type II—high insertion of the ureter with angulation and valve formation.

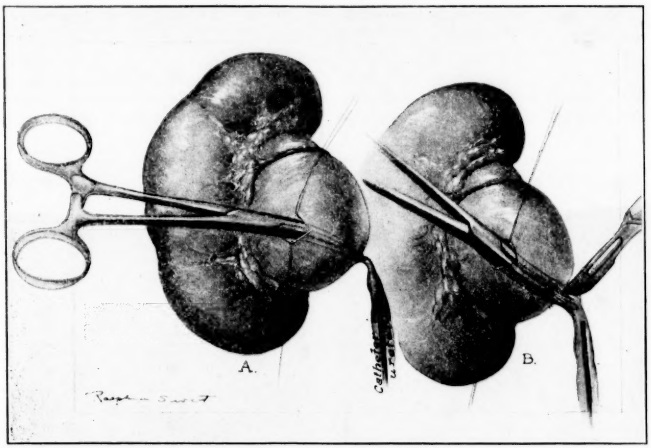


FIGURE 4. *Operation for Type I Hydronephrosis.*

These drawings and those in Figures 5 and 6 illustrate the technic of the operation. Through a pyelotomy incision the strictured ureteropelvic junction is dilated with a hemostat, and externally several parallel vertical incisions are made down to the mucosa as in the Rammstedt operation.

ureterolysis. This is followed by one or the other operation, depending on whether the hydronephrosis is Type I or Type II. In either case no sutures are used, and the ureteropelvic opening is maintained by adequate splinting and nephrostomy drainage, the most important single element in obtaining a successful result. I should not eschew the use of sutures entirely, but wish particularly to emphasize the relative importance of splinting. No matter how generous the surgeon is in the use of sutures in plastic repair, the outcome is likely to be a failure unless he makes use of splinting; conversely, if he places his dependence on adequate splinting the result will almost certainly be successful even though he uses no sutures at all. The value of the ureteral splint has been emphasized by Peck,[8] and later by Harris,[9] Cabot,[10] Moore,[11] Sargent,[12] Priestley[13] and others, but has not received the attention it deserves. It should be maintained in situ postoperatively for ten days to three weeks or even longer, depending on the extent of deformity and infection. It is hardly necessary to state that infection should be eliminated, so far as possible, by preoperative treatment. If ptosis is present, nephropexy should be included in the operative treatment. In the occasional case of slight hydronephrosis of a possible dynamic nature where mechanical obstruction is not a clear-cut factor, I have also performed renal sympathectomy in order to make doubly sure of relieving the patient of pain. In other cases that do not run quite true to type, additional measures, such as excision of a portion

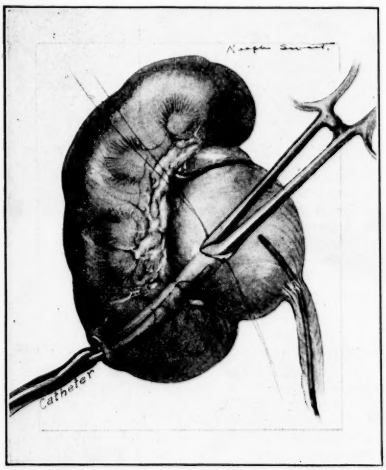


FIGURE 5. *Operation for Type I Hydronephrosis.*

The point of the hemostat is pushed out through the lower major calyx and a double-eye Robinson catheter, No. 18 or 20 Fr., is pulled into the pelvis.

of the hydronephrotic pelvis where it is excessively redundant, may be indicated.

The procedures here advocated are characterized by their simplicity and the ease and speed with which they can be performed. Difficult technical practices and complicated methods of suture are entirely eliminated. One may well question the value of sutures in the attenuated tissues of the hydronephrotic pelvis complicated by the presence of urine and more or less infection. In those cases of elaborate plastic operation and delicate suturing in which the outcome has been favorable, the result may well be attributed to the adequate use of splinting rather than to the plastic procedure itself.

The following report will serve to illustrate my point.

G. C., a 25-year-old woman, had a congenital solitary left kidney with advanced hydronephrosis. She entered the hospital in an almost moribund condition, due to acute fulminating pyelonephritis with fever, nausea and vomiting, and repeated chills. A No. 7 Fr. whistle-tip ureteral catheter was successfully passed cystoscopically to the kidney pelvis and was left in place for drainage. There was moderate improvement, with the aid of repeated clyses and urinary antiseptics, but on the whole the course was stormy for the next 2 weeks, with the temperature never normal. Eventually it became impossible to get a catheter back through the obstruction at the ureteropelvic juncture after it had become displaced, and the patient promptly lapsed into her original almost moribund state, with high fever and chills.

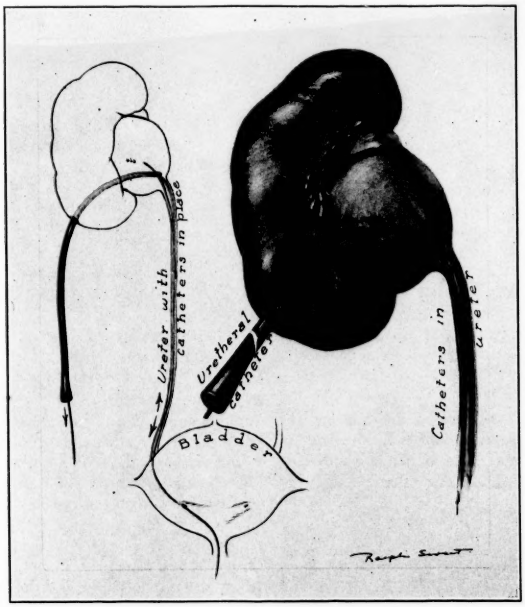


FIGURE 6. *Operation for Type I Hydronephrosis.*

These show the conclusion of the operation, with the method of nephrostomy drainage and ureteral splinting. Prior to operation a No. 7 Fr. ureteral catheter is passed to the kidney through the cystoscope. After the Robinson urethral catheter is drawn into the pelvis a second No. 7 Fr. ureteral catheter is passed in through the Robinson catheter, emerging from one of the openings, and is passed down the ureter alongside the ureteral catheter already in place. This provides adequately for two-way drainage and irrigation of the pelvis, and doubly splints the ureter.

An emergency operation was performed, with the sole purpose of providing nephrostomy drainage with all possible dispatch because of the patient's precarious condition. The kidney was quite large, grayish, soft and flabby, and the cortex was spotted with innumerable small, whitish abscesses the size of pinheads. The perirenal and peripelvic tissues were very edematous and friable, and easily dissected away, permitting an excellent view of the pelvis and ureteropelvic outlet. The condition proved to be a characteristic Type II hydronephrosis, with high insertion of the ureter and an obstructing vascular band, containing a rather large vein. The band was quickly resected, the pelvis opened and ureteropelvic junction incised downward. Nephrostomy drainage and ureteral splinting (as in the Type II operation) concluded the operative procedure. No sutures were used, first because of the need for haste, and secondly because the tissues were too soft and friable to hold a suture. My plan was first to provide nephrostomy drainage, and if the patient did not succumb to perform some sort of plastic operation at a later date.

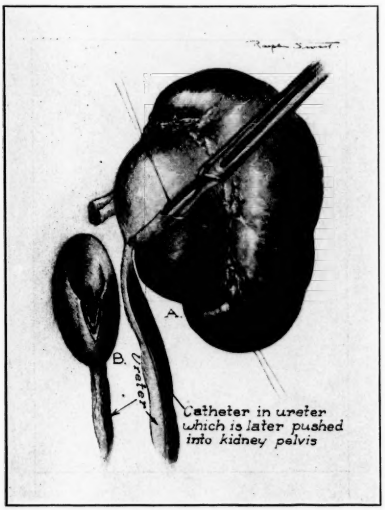


FIGURE 7. *Operation for Type II Hydronephrosis.*

This drawing and that in Figure 8 illustrate the technic of the operation. A No. 7 Fr. ureteral catheter is passed up the ureter prior to operation. A pyelotomy incision is made, and the valve-like partition caused by the high insertion is incised downward with scalpel or scissors as far as necessary to provide a wide opening at the ureteropelvic junction, with dependent drainage. The end of the catheter, if not already in the pelvis, is advanced until it is well within.

Immediately following operation the patient began to improve. The nephrostomy drainage and splinting were maintained for 3 weeks. After removal there was no leakage of urine through the wound, which promptly healed, and the patient made a rapid recovery. Figure 10*A* shows a retrograde pyelogram before operation, while Figure 10*B* shows an excretion urogram demonstrating the condition of this solitary kidney 6 months later. The urine was sterile on culture and free from pus cells. A phenolsulfonephthalein test showed an output of 60 per cent in 2 hours. Three years later the patient wrote that she had remained perfectly well.

COMMENT

The ultimate result of the preliminary drainage operation in this case was so satisfactory that a secondary plastic operation appeared to be entirely unnecessary. This experience presented considerable food for thought, and raised a question as to the rationale of the plastic operations on hydronephrosis that are in general use at the present time. I question the necessity for complicated plastic procedures with elaborate suturing, which are more or less time-consuming, and one questions how well such sutures hold in the attenuated and devitalized tissues of the obstructed pelvis in the presence of urine and varying degrees of infection. I reiterate that reliance on adequate splinting rather than sutures will give a higher percentage of successful end results. An orthopedist would not think of reducing a fracture without a splint to hold it in proper alignment during the healing process. This orthopedic principle can be borrowed by the urologist to good advantage. McArthur[14] has shown that the splint can be successfully used to bridge a hiatus in the ureter where there has been an interruption of its continuity, and I[15] have stressed the value of the ureteral splint following removal of calculi from the kidney pelvis or upper ureter which is obstructed or distorted and kinked by dense adhesions. It may occasionally be advantageous to use sutures in conjunction with splinting, but they are of secondary importance and should be employed sparingly, and one should meticulously approximate the cut edges, avoiding puncture of the mucosa if possible. No. 00000 chromic catgut appears to be the most suitable material for plastic work.

Judgment in the selection of cases for plastic operation deserves a word of comment. Functional tests conducted preoperatively are generally misleading, as well shown by Schulhof and Cabot.[16] Even in the presence of a normal mate, nephrectomy should never be decided on unless the kidney has been actually viewed at operation and found to be only a thin-walled sac without an appreciable amount of parenchyma, or unless infection has destroyed the parenchyma beyond hope of recovery. Preoperative functional tests may indicate more or less complete functional impairment, yet at operation a considerable amount of normal-looking parenchyma may be found, which will surprise one with the degree of functional resto-

ration that will occur following a successful plastic operation, even in the presence of a normal mate.

This paper has been purposely limited to the discussion of non-calculous obstructions at the ureteropelvic juncture. It should not be necessary to emphasize that hydronephrosis may be due to form of bands, adhesions, anomalous vessels, ptosis and so forth, as previously enumerated. Extrinsic factors may alone cause hydronephrosis, and their removal will result in cure without the necessity for plastic operation in the absence of intrinsic factors.

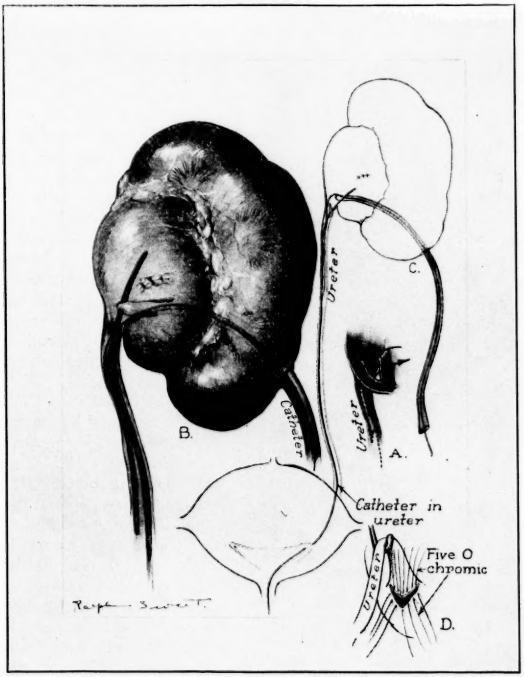


FIGURE 8. *Operation for Type II Hydronephrosis.*

This drawing illustrates the method of nephrostomy drainage and double ureteral splinting, which is the same as in the Type I operation. The entire procedure is easily and quickly performed. No sutures need be used except to close the pyelotomy incision, and even these can be dispensed with. Nephrostomy drainage is preferable to pyelostomy drainage because the renal parenchyma splints the tubes and maintains them in accurate position with a greater degree of certainty. Sutures as shown in D *are optional.*

a great variety of obstructions at any point below the level of the renal pelvis, even to the external urethral meatus, and that accurate differential diagnosis requires their elimination before resorting to plastic surgery on the ureteropelvic juncture.

Types I and II hydronephrosis may be properly termed intrinsic types. They are usually complicated by one or more extrinsic factors in the

The question arises as to whether hydronephrosis due to obstruction at the ureteropelvic juncture can ever be relieved by cystoscopic dilatations. Rarely, Type I hydronephrosis can be relieved in this way, provided there are no complicating extrinsic factors, but most of the cases will require surgical relief.

A more general comprehension of the fact that

the vast majority of cases of hydronephrosis fall into two groups or types, susceptible to correction with a fair degree of certainty by one or the other of two simple types of operation, should result in fewer nephrectomies and in a higher percentage of successful end results in the plastic repair of hydronephrosis.

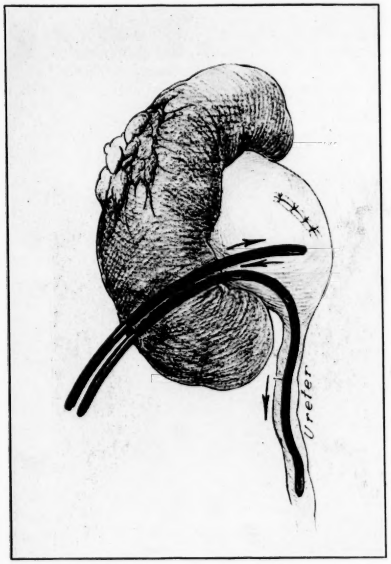


FIGURE 9. *An Alternative Method of Nephrostomy Drainage and Ureteral Splinting.*

Following the necessary plastic procedure, two small Robinson urethral catheters, No. 10 or 12 Fr., may be drawn into the pelvis and one passed down the ureter safely beyond the point of obstruction. Additional openings are made in these catheters at strategic points, as shown in the sketch.

CONCLUSIONS

The present status of the surgical treatment of hydronephrosis is briefly reviewed. Nephrectomy is still too often resorted to because of lack of confidence in plastic operations. The principal types of plastic operations in current usage are described and illustrated. Statistical summaries of end results show a relatively high percentage of failures, and point to the necessity for a re-evaluation of the types of hydronephrosis and standardization of methods of surgical treatment.

Hydronephrosis due to ureteropelvic obstruction falls into two general groups, described as Types I and II.

Two operative procedures are proposed, which seem best adapted to the surgical treatment of hydronephrosis. They are characterized by simplicity and ease of performance, with emphasis on the necessity for nephrostomy drainage and ureteral splinting, with elimination of sutures.

Experience with these procedures suggests the possibility of eliminating elaborate plastic operations and the delicate suturing that they entail, in favor of simpler procedures which will decrease the number of nephrectomies for hydronephrosis and give greater assurance of successful end results.

450 Sutter Street.

REFERENCES

1. Mathe, C. P.: Plastic operations on the upper ureter and pelvis for hydronephrosis. *History of Urology.* Edited by B. Lewis, E. G. Ballenger, W. A. Frontz and H. G. Hamer. 2 vol. 746 pp. Baltimore: Williams & Wilkins Co., 1933. Pp. 329-343.
2. Trendelenburg, F.: cited by Fenger.[4] P. 900.
3. Küster, E.: Ein Fall von Resektion des Harnleiters. *Beilage z. Zentralbl. f. Chir.* 19:32-110, 1892. Ein Fall von Resection des Ureter. *Arch. f. klin. Chir.* 44:850-854, 1892.
4. Fenger, C.: Operation for the relief of valve-formation and stricture of the ureter in hydronephrosis or pyonephrosis. *The Collected Works of Christian Fenger.* 2 vol. 1050 pp. Philadelphia and London: W. B. Saunders Co., 1912. Pp. 687-704. *J. A. M. A.* 22:335-343, 1894.
5. Ormond, J. K.: End-results of plastic operations on the kidney pelvis for hydronephrosis. *Am. J. Surg.* 38:70-79, 1937.
6. Young, H. H.: Hydronephrosis and pyonephrosis: conservative treatment. *S. Clin. North America* 16:1219-1230, 1936.
7. Lubash, S.: Uretero-pyeloneostomy for hydronephrosis: a new operative technique. *J. Urol.* 34:222-229, 1935.
   Lubash, S., and Madrid, A.: Uretero-pyeloneostomy for hydronephrosis: with case and final reports. *Ibid.* 38:634-642, 1937.
8. Peck, C. H.: Treatment of obstructions of the upper ureter and early hydronephrosis. *Ann. Surg.* 83:260-266, 1926.
9. Harris, A.: The problem of non-calculous ureteropelvic obstruction. *Ann. Surg.* 102:1050-1058, 1935.
10. Cabot, H.: discussion of Pilcher, F.: The treatment of bilateral congenital hydronephrosis. *Proc. Staff Meet., Mayo Clin.* 12:279-283, 1937.
11. Moore, T. D.: The diagnosis and management of hydronephrosis secondary to ureteropelvic obstruction of the noncalculous type. *Am. J. Surg.* 38:101-115, 1937.
12. Sargent, J. C.: Conservative surgery in hydronephrosis. *J. Urol.* 38:680-687, 1937.
13. Priestley, J. T.: The conservative surgical treatment of non-calculous hydronephrosis. *Surg., Gynec. & Obst.* 68:832-841, 1939.
14. McArthur, L. L.: New and simple repair of ruptured or strictured ureters. *Surg., Gynec. & Obst.* 41:719-721, 1925.
15. Gibson, T. E.: The ureteral splint: its value in the surgery of renal calculi. *J. Urol.* 42:1169-1175, 1939.
16. Schulhof, M. G., and Cabot, H.: The effect of surgical drainage on kidneys declared functionless by present tests of renal function. *Surg., Gynec. & Obst.* 65:188-194, 1937.

DISCUSSION

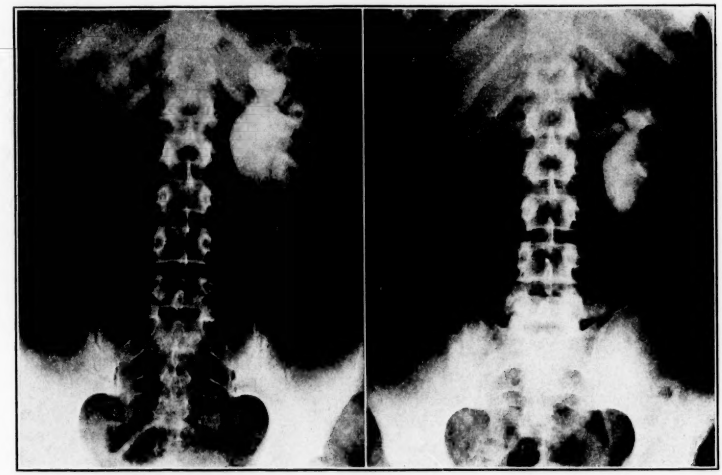
DR. CLYDE L. DEMING, New Haven, Connecticut: I have for a long time been looking at hydronephrosis simply from an operative standpoint. In 1925 or 1926 I reimplanted a ureter in the wife of a young doctor friend of mine. He was not a urologist but a surgeon, and he knew quite a bit about surgery of the kidney. The morning after the operation Dr. Quinby published a paper in which he asserted that this operation should never be performed. Fortunately, however, this case proved to be one of the most successful I had ever treated. I encountered a large osteum at the point of anastomosis. The patient had had frequent urinations since childhood and had been through one pregnancy. She has remained free from infection.

There is nothing more intriguing to me than the correction of hydronephrosis, and I am indebted to Dr. Gibson in reducing this treatment to logical terms and rendering it both simple and efficacious.

Dr. Samuel N. Vose, Boston: Dr. Gibson's operations seem logical. I have used the Rammstedt operation with satisfaction. I have employed for a splint, with satisfactory results, a single catheter in the cortex, with holes cut corresponding to the pelvis.

I should like to mention the significance of minor degrees of hydronephrosis as regards pain and a predisposition to infection and stone formation. Compensation has been widely recognized. Compensated bladders carry a good deal less residual urine in the presence of bladder-neck obstruction than do decompensated ones. The same thing applies to the kidney pelvis. In the presence of a good deal of obstruction, extrarenal pelves usually show extensive hydronephrosis, while in the intrarenal pelves the kidney cortex is more apt to suffer.

Dr. Gibson (closing): It may be that we need a hydronephrosis registry, as we need a carcinoma registry, in order properly to evaluate and standardize the operations for plastic repair of hydronephrosis. I have been appalled at seeing many doctors, not only general surgeons but also urologists, remove fairly good kidneys capable of a marked amount of functional restitution rather than attempt a plastic operation, because they lacked confidence in it. Certainly if one lacks confidence one is inclined to do a nephrectomy, because if a plastic operation is not successful the patient may require a second operation involving nephrectomy, which does not redound to the credit of the surgeon. Appraisal of results attendant on adherence to the principles of plastic repair above outlined limits the indications for nephrectomy to those kidneys which are hopelessly destroyed.



A B

Figure 10. *Results of Operation.*

A — photograph of retrograde pyelogram in a twenty-five-year-old woman, with a Type II hydronephrosis of a congenital solitary left kidney complicated by acute pyelonephritis. B — photograph of excretion urogram six months after operation. There were excellent restoration of function, complete elimination of infection and adequate dependent drainage.

Dr. Fletcher H. Colby, Boston: Dr. Gibson has made an original contribution. The successes I have had in plastic operations on the ureteropelvic junction have been achieved with reimplantation of the ureter or with the Finney pyeloplasty. I have had no success with the Rammstedt operation, very likely because I do not know how to do it well enough. Can Dr. Gibson discuss the theory of renal counterbalance? How is one to tell when a kidney has been badly damaged and its mate has taken over its function. I should also like to know how much infection one can have and still do a successful plastic operation.

Dr. Augustus Riley, Boston: I should like to ask whether Dr. Gibson has ever encountered sloughing of the junction in performing a ureteral operation.

Dr. Colby spoke of reimplantation. In the original Küster operation the ureter is resected and reimplanted in the most dependent portion of the pelvis. The only case in which this procedure is followed is that of an anomalous vessel, an artery that is too large to sacrifice safely. This does not occur very often. Here also the key to success is adequate splinting and nephrostomy drainage. I have not seen any sloughing of the mucosa as a result of splinting.

It has been asked, In the presence of how much infection should one attempt a plastic operation? Of course, one should try to clear up infection prior to operation, but I should not hesitate to operate in the presence of considerable infection, relying on ureteral splinting and nephrostomy drainage.

APPENDICES EPIPLOICAE*

GEORGE A. MOORE, M.D.†

BROCKTON, MASSACHUSETTS

THE early literature regarding appendices epiploicae has been reviewed in considerable detail by several writers in the past two decades, notably Hunt,[1] Klingenstein[2] and Patterson.[3] Only a very brief summary therefore will be given here of the more important contributions to this subject in the past.

In 1703 Littre[4] discovered a pea-sized foreign body in the abdominal cavity that was thought to be the remains of an appendix epiploica; Cruveilhier[5] (1849) and Deville[6] (1851) also described foreign bodies in the abdominal cavity, which were assumed to have a similar origin.

In 1863 Virchow[7] gave a detailed description of the formation and composition of foreign bodies in the abdomen and claimed that the majority had their origins in appendices epiploicae.

In 1905 Riedel[8] published the first comprehensive study of the clinical aspects of 8 cases illustrating the various pathologic conditions associated with appendices epiploicae.

Robinson's[9] thesis, published in 1908, on the anatomy and pathology of the "seroappendices," is the most painstaking study of the subject that has yet appeared. He stated that the dog, cat, rabbit and rat have no seroappendices, but that the anthropoid ape has seroappendices similar to those found in man. Contrary to other writers, he stated that the appendices are found in the fetus at two and three months, as well as in the newborn. Robinson's detailed description of the anatomy, physiology and pathology of appendices epiploicae is still generally accepted.

Anatomically appendices epiploicae are pedunculated tabs of fat attached to the colon, covered only with peritoneum, which vary greatly in size, shape and number. They extend from the cecum to the rectum, usually in two rows, one in relation to the anterior tenia and the other in relation to the posterointernal tenia. The largest appendices are usually found on the sigmoid. They are true hernias of the visceral peritoneum, filled with fat.

The physiological function of appendices epiploicae has never been definitely established. Robinson[9] has suggested that they are a factor in the movements of fluids in the colon.

The pathologic conditions which involve appendices epiploicae and the approximate number of times they have been reported are as follows: foreign bodies, 15; intra-abdominal torsion, 43; intrahernial torsion and strangulation, 15; intrahernial incarceration, 16; and adhesions resulting in intestinal obstruction, 7. As additions to these I submit herewith 2 cases of intra-abdominal torsion, 1 case of adhesion incarceration in a hernial sac, causing strangulation of a loop of the sigmoid, and 2 cases of intra-abdominal adhesions resulting in acute intestinal obstruction.

Foreign bodies which lie in the abdominal cavity or in a hernial sac originate in most cases from gradual torsion on appendices epiploicae and give rise to no symptoms. It is quite probable that most cases of acute torsion require early operative relief and hence do not result in the formation of foreign bodies. In Virchow's[7] case, death resulted from peritonitis apparently from a foreign body originating in an appendix epiploica attached to the vermiform appendix. Riedel[8] cited a case with symptoms of "gall-bladder adhesions" in which only fatty foreign bodies were found. He also described a patient with abdominal pain from a hernia, who was relieved by removal of a small, fatty foreign body from the hernial sac. The potential danger of infection from any foreign body in the abdomen is generally recognized.

Torsion occurs more frequently than any other pathologic process in appendices epiploicae. Chronic and acute types of torsion are found at operation; the acute torsion is more frequently observed, as it is commonly accompanied by urgent symptoms which necessitate operation.

The chronic type is probably the cause of many foreign bodies in which a gradual saponification of the fat content has occurred, followed by calcification or the formation of pseudo-cartilaginous bodies. Chronic torsion is the cause of certain types of adhesions producing intestinal obstruction, which will be described later. It is quite probable that a certain number of cases with unexplained mild attacks of abdominal pain are due to chronic torsion of an appendix, which terminates in a foreign body or adhesions.

Many patients in whom acute torsion is found at operation give a history of numerous attacks of abdominal pain in the past. Cases of torsion have been reported (Hunt[1]) in which no history of acute symptoms was obtained and the strangulated appendix epiploica was an incidental finding at operation. In most patients, however, there

*Read by title at the annual meeting of the New England Surgical Society, Salem, Massachusetts, September 29-30, 1939.

†Surgeon, Moore Hospital, Brockton, Massachusetts.

is a history of acute, localized abdominal pain with marked tenderness and muscle spasm, simulating appendicitis, an acute lesion of the gall bladder or diverticulitis. The late stages may be complicated by infection, gangrene or abscess, with the typical clinical signs of localized or diffuse peritonitis (Klingenstein,[2] Fallon,[10] Grigsby,[11] Rankin, Bargen and Buie[12] and Black[13]).

The cause of torsion of an appendix epiploica is still a matter of conjecture. Congestion in one in which the vein is longer than the artery has been suggested (Payr[14]), as has an abnormally large appendix on a long pedicle (Morestin[15]). The following two cases are illustrative of this condition.

Case 1. V. F., a 76-year-old married woman, was admitted to St. Luke's Hospital, Middleboro, Massachusetts, on December 18, 1937. She had had a vaginal hysterectomy at another hospital in 1905, an excision of a cyst of the right ovary at the same hospital in 1905 and a cholecystostomy at still another hospital in 1911. The patient had enjoyed fair health with no definite abdominal symptoms for the previous 25 years. About 12 hours before admission she was suddenly seized with excruciating non-radiating pain in the right lower quadrant of the abdomen. She had had no nausea or vomiting. The temperature was normal, the white-cell count 8000, and the blood smear normal; the urine contained a rare red blood cell in the sediment.

On physical examination the patient was moderately pale. The pupils, mouth, throat, heart and lungs were not remarkable. The blood pressure was 120/90. The abdomen was quite distended, and there were linear scars in the right upper quadrant and the right suprapubic region. Marked tenderness and spasm were noted over a small area on the right side of the abdomen on a level with the umbilicus. Pelvic and rectal examinations revealed nothing abnormal.

Exploration revealed a pyramidal dark-red mass about 2.5 cm. in diameter attached by a short pedicle to the ascending colon. The pedicle was twisted three full turns. Excision of the mass was followed by an uneventful convalescence. The pathologist reported that the specimen consisted of fatty tissue showing hemorrhage and acute inflammation, a condition compatible with a damaged portion of an appendix epiploica.

The discharge diagnosis was torsion of an appendix epiploica of the ascending colon.

Case 2. G. E. J. (No. 10,017), a 28-year-old married woman, was admitted to the Moore Hospital, Brockton, Massachusetts, on April 12, 1938. The past history was unimportant. During the previous 5 years the patient had experienced numerous attacks of moderate pain in the right lower quadrant of the abdomen, which lasted 4 or 5 hours and were accompanied by nausea but no vomiting or apparent fever. She had had no indigestion, the bowels were normal, and menstruation was regular and normal. About 17 hours prior to entry pain in the right lower abdominal quadrant gradually developed; this persisted with increasing severity up to admission. The patient vomited twice several hours after the onset of the pain.

Physical examination was essentially negative except for marked tenderness and rigidity of the abdominal wall to the right of the umbilicus, which extended to the right flank. The temperature was normal, and the white-cell count 7500. The urine was normal except for a few red blood cells in the sediment.

At operation a dark-purple appendix epiploica was found on the outer aspect of the head of the cecum, which was twisted four full turns on its pedicle. The vermiform appendix was moderately inflamed and thickened. Both were removed, and the patient made a good recovery.

The discharge diagnosis was torsion of an appendix epiploica of the outer aspect of the head of the cecum and acute catarrhal appendicitis.

The occurrence of appendices epiploicae in hernial sacs has been reported in 31 cases, being next in frequency to intra-abdominal torsion. The most frequent resting-place of these migratory fatty tabs is the sac of a left inguinal hernia, apparently on account of the large number of such appendices on the sigmoid and the greater range of motion of this part of the colon. They have also been found in right inguinal, femoral and umbilical hernial sacs.

Adhesions and incarcerations of appendices epiploicae occur in hernias of long standing in which the sac or contained appendix has undergone inflammatory changes brought about by chronic infection or irritation such as that produced by a truss. In these cases the adherent appendix may be the cause of strangulation of the sigmoid, as occurred in Case 3. In long-standing hernias, torsion is not found so frequently as is incarceration, presumably because of the presence of adhesions.

Case 3. J. A. R. (No. 8309), a 76-year-old man, entered the Moore Hospital, Brockton, Massachusetts, on October 22, 1934. About 45 years previously he had had an attack of acute abdominal pain, lasting several days and finally relieved by laxatives. No definite diagnosis of this condition had been made. Soon after the above attack he had noticed a left inguinal hernia, which had gradually increased in size in the intervening years. The hernia had "come down" many times, but he had always been able to reduce it. His general health had been good. Three days before admission he had had difficulty in evacuating his bowels, but finally succeeded after two enemas. The previous night, about 12 hours before admission, he had been seized with severe pain in the left lower quadrant; this had continued.

On physical examination the patient was moderately pale. The blood pressure was 175/80. The abdomen was considerably distended, and there was considerable tenderness in the left lower quadrant. A small very tense, irreducible left scrotal hernia was found. When the hernial sac was opened, a rather large appendix epiploica was seen attached to the fundus. The pedicle of the appendix was very taut, and it was evident that it was a factor in pulling a loop of sigmoid into the sac and in preventing its reduction. The appendix epiploica was excised, and reduction and repair of the hernia was carried out in the usual way.

The discharge diagnosis was appendix epiploica of the sigmoid with incarceration in a left scrotal hernia.

Inflammation of appendices epiploicae, in rare cases, may result in adhesions which cause in-

testinal obstruction. Whether the inflammation is preceded by torsion has not been determined. In certain cases, torsion is definitely the cause, as it is found that the appendix has dropped off, that the proximal stump has adhered to the parietal peritoneum, mesentery or intestine, and that a loop of intestine has slipped in back of the cord thus formed and has thus become strangulated. In one of my patients (Case 5) fully a third of the small intestine was strangulated in this way. The other two processes causing obstruction are adherence of an appendix epiploica to the parietal peritoneum or viscera and adherence of two inflamed appendices across a loop of intestine. Baumeister, Hargens and Morsman[16] collected 6 cases of intestinal obstruction from the literature, and added 1 to the list. The following 2 cases occurred in my practice, bringing the total number to 9.

Case 4. M. A. P. (No. 7543), a 75-year-old married woman, entered the Moore Hospital, Brockton, Massachusetts, on May 3, 1933. She had had a total hysterectomy at another hospital in 1905. There had been no serious illness since operation, but she had been quite constipated in recent months. About 30 hours before admission she was seized with severe epigastric pain, nausea and vomiting and complained of marked tenderness in the left lower quadrant, which had persisted.

On physical examination the patient was of good color. The blood pressure was 124/90. The abdomen was moderately distended and extremely tender, with spasm over the entire left side. The temperature was 97.6°F., and the white-cell count 10,500. A flat x-ray plate of the abdomen and a barium enema showed evidence of small-bowel obstruction.

At operation an appendix epiploica was found on the outer aspect of the descending colon; it was attached to the parietal peritoneum in the left flank. Beneath the band thus formed about 45 cm. of lower ileum was strangulated. When the band was severed the strangulated bowel appeared viable. Enterostomy was done above the site of the obstruction, which emptied the obstructed intestine. The patient appeared to be making a good recovery for 4 days and then developed pneumonia and died seven days after operation.

The discharge diagnoses were strangulation of a loop of ileum by a fibrous band resulting from an adhesion of an appendix epiploica to the parietal peritoneum in the left flank, and pneumonia.

Case 5. P. W. (No. 8045), a 23-year-old unmarried woman, entered the Moore Hospital, Brockton, Massachusetts, on April 17, 1934. Her general health had been excellent in the past. The bowels were regular, but the catamenia were irregular and accompanied by pain. About 5 months previously she had had an attack of epigastric pain, which was followed by a bowel movement which contained bright blood. Gastrointestinal x-ray films were taken, with inconclusive findings. Since then she had had two similar attacks. About 6 hours before admission, while straining at stool, she was seized with severe epigastric pain, nausea and vomiting. She became very pale, was faint, had a subnormal temperature and continued to vomit until she was admitted to the hospital.

On physical examination there was marked pallor; the skin was moderately cool. The blood pressure was 100/60. The temperature was 96.8°F., and the white-cell count 11,000; the urine was normal. Nothing abnormal was found except moderate distention of the lower abdomen, with tenderness in the left lower quadrant.

Following the usual preoperative therapy, a left paramedian lower abdominal incision was made. Approximately a third to half the small intestine was strangulated by a taut, small cord arising in the lower descending colon and attached to the base of the mesentery of the small intestine. No appendix epiploica was found at the distal end of this cord, but from its site of origin the latter was assumed to be a greatly stretched pedicle of an appendix epiploica. The band was excised, the strangulated intestine proved to be viable, and convalescence was uneventful.

The discharge diagnosis was strangulation of the small intestine by a fibrous band resulting from an adhesion of an appendix epiploica.

Summary

It has been suggested by Patterson[3] that diseases or, better, pathologic conditions of appendices epiploicae occur more frequently than are reported in the literature. These conditions may well account for many cases of intestinal obstruction due to congenital bands of undetermined origin, and for certain cases explored for an acute abdominal episode in which no pathologic lesion is found.

An attempt has been made to emphasize some of the important facts in the literature regarding these uncommon lesions of appendices epiploicae, in the hope that a search will be made for them in acute abdominal conditions without obvious cause.

167 Newbury Street.

References

1. Hunt, V. C.: Torsion of appendices epiploicae. *Ann. Surg.* **69**:31-46, 1919.
2. Klingenstein, P.: Some phases of the pathology of appendices epiploicae: with report of four cases and review of the literature. *Surg., Gynec. & Obst.* **38**:376-382, 1924.
3. Patterson, D. C.: Appendices epiploicae and their surgical significance: with report of three cases. *New Eng. J. Med.* **209**:1255-1259, 1933.
4. Littre: cited by Harrigan, A. H.: Torsion and inflammation of the appendices epiploicae. *Ann. Surg.* **66**:467-478, 1917.
5. Cruveilhier: mentioned by Harrigan.[4]
6. Deville: mentioned by Harrigan.[4]
7. Virchow, R.: cited by Harrigan.[4]
8. Riedel: cited by Harrigan.[4]
9. Robinson, R.: *Anatomie et pathologie des sero-appendices.* 99 pp. Paris theses, 1908.
10. Fallon, M.: discussion of Patterson.[3]
11. Grigsby, G. P.: cited by Rankin, Bargen and Buie.[12]
12. Rankin, F. W.; Bargen, J. A., and Buie, L. A.: *The Colon, Rectum and Anus.* 846 pp. Philadelphia: W. B. Saunders Co., 1935.
13. Black, S. O.: Torsion of appendices epiploicae. *South. M. J.* **16**:35-37, 1923.
14. Payr, E.: Ueber die Ursachen der Stieldrehung intraperitoneal gelengener Organe. *Arch. f. klin. Chir.* **68**:501-523, 1902.
15. Morestin, H.: Torsion d'un appendice épiploïque du gros intestin. *Bull. Soc. anat. de Paris* **87**:391-394, 1912.
16. Baumeister, C.; Hargens, C. W., and Morsman, C. F.: Obstruction due to appendices epiploicae. *Ann. Surg.* **107**:153, 1938.

REPORT ON MEDICAL PROGRESS

PATHOLOGY

TRACY B. MALLORY, M.D.*

BOSTON

HYPERTENSION AND RENAL DISEASE

THE CLOSE relation between renal disease and elevation of the arterial blood pressure has been common knowledge for three quarters of a century, but only within the last six years has convincing experimental evidence regarding the possible mechanism of this relation appeared. Through the intervening period innumerable clinical and anatomical studies served gradually to distinguish between the primary nephropathies with secondary elevation of the blood pressure and a syndrome which became known as "essential hypertension," in which high blood pressure preceded by long periods the development of any other clinical or functional evidence of renal impairment. Clinicopathological correlation, however, clearly demonstrated that very few of these patients at postmortem examination failed to show extensive arteriolar disease, particularly within the kidneys, though functionalist and morphologist futilely battled for decades over the precedence of the hypertension or the arteriolar degeneration.

Through the period from 1925 to 1935 pathological interest focused sharply on the details of the vascular lesions in nephrosclerosis and on their correlation with clinical types of hypertension. A "benign" and a "malignant" form were widely recognized, and exhaustive studies[1-5] of long series of cases were published affirming or denying the identity of the two types and the possibility of accurate clinicopathological correlation. The difficulties of histological distinction were attested by the considerable variation of the supposedly pathognomonic criteria, various authors emphasizing in turn periarterial granulomatous reactions,[1] necrotizing arteriolitis,[3] endarteritis, alterative glomerulitis,[5] and so forth as of pre-eminent importance, till the intricacies dazed even the professional morphologist.

In 1934 attention was suddenly shifted in a more profitable direction by the publication by Goldblatt and a group of associates[6-16] of the first of a series of experiments on the production of hypertension and its physiological mechanism. If a clamp was placed on the renal artery which narrowed but did not occlude the latter, the systemic blood pressure rose significantly for a period of weeks. If the clamp was removed or the ischemic kidney resected the blood pressure fell to the previous control level. The hypertension was therefore clearly dependent on the presence in the body of ischemic renal tissue. Bilateral narrowing of the renal arteries or unilateral narrowing with nephrectomy of the opposite sound kidney produced severe and apparently permanent hypertension. The experiments were quickly and widely confirmed,[17, 18] and a wealth of investigation has been stimulated which may well prove to be only in its infancy. New methods of producing renal ischemia and consequent hypertension have been developed, such as exposure of the kidneys to x-rays (Hartman[19]) and enveloping them in a bag of cellophane (Page[20]), which provokes the formation of a dense fibrous constricting capsule. Removal of the encapsulated kidney promptly brings the blood pressure back to normal, just as in the Goldblatt experiments.

It is clear that the nervous system is not directly responsible for the genesis of the hypertension, since renal denervation,[21, 22] total sympathectomy[23] or total destruction of the spinal cord by pithing[24] does not prevent its development.

With a neural mechanism eliminated a humoral one seemed inescapable, and imaginations quickly turned to the possibility of the elaboration of pressor substances within the kidney. As far back as 1898 Tigerstedt and Bergman[25] had described a protein substance with a marked pressor action extractable from the renal cortex, which they named "renin." Forty years later, independently, but in quick succession, Landis, Montgomery and Sparkman,[26] Williams, Harrison and Mason[27] and Corcoran and Page[28] renewed these experiments and have obtained extracts with similar properties from the renal cortex. Since extracts of a great variety of tissues are known frequently to have depressor and occasionally pressor effects, the demonstration by Landis et al.[26] that this substance raises blood pressure without lowering skin temperature in contrast to all previously known pressor substances possibly extractable from tissues, such as adrenaline, pitressin, tyramine and so forth, is of fundamental importance. Confirmatory evidence that renin action is different from that of other pressor substances has been

*Assistant professor of pathology, Harvard Medical School; director, Department of Pathology and Bacteriology, Massachusetts General Hospital, Boston.

obtained by demonstrating the ineffectiveness of cocaine and other drugs either in increasing or decreasing its action.[29] Helmer and Page[30–32] have developed a method for producing renin in large amounts, and have been able to purify it and to show that renin itself in Ringer's solution has no pressor effect, but by interaction with a component of the blood serum (rather unfortunately called "renin activator") forms a third product designated angiotonin which appears to be the actual vasoconstrictive and pressor substance. Renin, they believe, is probably an enzyme since it is a protein, is thermolabile, reacts slowly with its substrate (renin activator) and is effective in small amounts in proportion to the substrate. Moreover, the renin-angiotonin relation is a double one, since renin not only forms angiotonin but will with further contact destroy it. Whether or not the pressor effect of the presence of ischemic renal tissue in the body is dependent on an intact endocrine system is still somewhat uncertain. Hypophysectomy probably diminishes but does not abolish the effect.[33] Bilateral adrenalectomy was found to abolish it, but the effect was cortical rather than medullary and the results with cortin and sodium substitution therapy have been variable.[34–36]

The application of this wealth of experimental data to human lesions is still far from clear. Excluding rare cases of chromaffin tumors of the adrenal medulla, it is doubtful if anyone to date has succeeded in isolating from the blood of hypertensive patients an effective pressor substance.[21] Even in dogs the results are equivocal. Houssay and Fasciolo[37] report immediate elevation of the blood pressure following transplantation of an ischemic kidney into the neck of a nephrectomized dog, whereas the transplantation of a normal kidney had no such effect. Williams and Grossman[28] claim to have obtained renin and an adrenalin-like substance from the renal vein following perfusion of the isolated kidney. Yet Collins and Hoffbauer[39] were unable to demonstrate increased pressor action in blood from the renal vein of a hypertensive dog. Direct proof that renin formation and absorption are increased in the hypertensive individual, either human or canine, is still lacking. Tempting as the hypothesis is, it would be foolish at the present time to give it blind credence.

Moritz and Oldt,[40] reviewing the field of arteriolar sclerosis and hypertension, with the advantage over previous investigators of following rather than preceding Goldblatt, have reported statistical data of great interest, based on a very careful comparison of 100 hypertensive with 100 non-hypertensive individuals. Arteriolar sclerosis may of course be widespread throughout the body in both groups. In all organs and tissues but one the distribution was essentially similar in each, though naturally more severe and extensive in the hypertensive group. In the kidney, however, almost all hypertensive cases (97 per cent) showed renal arteriolar sclerosis in some degree, whereas in the control group only 12 per cent showed even mild arteriolar changes and only 2 per cent changes of moderate severity. These figures approximate closely those of previous investigators. The parallelism between hypertension and obliterative disease of the small renal vessels is impressive though not absolute. No comparable correlation could be found in the case of any other organ or tissue. The anatomical basis for renal ischemia was therefore present in the vast majority of the hypertensive patients and absent in an almost equal proportion of non-hypertensive patients. Even in the 3 cases of hypertension without arteriolar disease the possibility of renal ischemia existed, since severe atherosclerosis of the major vessels including the renal arteries and their main branches was present. It must be pointed out, however, that except in the case of major obliterative lesions the appearance of a vessel post mortem is not an altogether reliable index of its capacity during life.[41, 42]

It is interesting in this connection that in Goldblatt's dogs the renal arterioles beyond the clamps do not undergo degeneration, whereas elsewhere in the body where the vessels are exposed to the increased intravascular tension arteriolar changes are widespread. Goldblatt has answered beyond doubt one question: prolonged hypertension will produce in the vessels exposed to it degenerative changes of types characteristic of human arteriolar lesions. By varying the degree of ischemia he could, in fact, vary at will the histologic reactions and produce either the hyalinization of benign sclerosis or the proliferative and necrotizing types of arteriolitis that have been widely considered to be typical of malignant hypertension. The latter appeared, in his experience, only in animals in which the ischemia was so great that renal insufficiency developed. His findings give strong support to those who consider benign and malignant hypertension merely opposite poles of a single disease entity, as against those who consider them to be similar but pathogenetically different disorders.

Of great interest is the observation of Moritz and Oldt[40] that in 4 cases the arteriolar degeneration was limited to one kidney. The analogy to the Goldblatt kidney is arresting. Of very similar import is the description by Butler[43] of cases of

children with unilateral pyelonephritis and hypertension in whom the hypertension was promptly and apparently permanently relieved by removal of the diseased kidney. A similar group of adult cases has been reported by Barker and Walters.[44]

This relation of pyelonephritis to hypertension has been extensively explored by Weiss and Parker.[45] From a study of pyelonephritides of varying duration they have set up gross and histological criteria for the recognition of the disease, even in its burnt-out stages. By application of these standards they have become convinced that a much higher proportion (30 to 35 per cent) of bilaterally contracted kidneys can be traced back to direct renal infection than has generally been believed, and that a considerable proportion of these cases develop hypertension. Experimental verification of their histological criteria of healed pyelonephritis will shortly be published by G. K. Mallory.[46]

Weiss and Parker have paid particular attention to the blood vessels in these kidneys. They believe that in many cases the arterioles are directly injured by the contiguous inflammatory reaction, with the production of vascular lesions indistinguishable except by their localization in inflamed areas from those of malignant nephrosclerosis. In cases of unilateral pyelonephritis such lesions are most marked in and may be restricted to the affected kidney. It seems probable, therefore, that they are primary and responsible for the hypertension by the production of ischemia. The possibility of a vicious circle is, of course, a tempting hypothesis.

Coronary Sclerosis and Infarction of the Heart

A section of last year's review[47] was devoted to anatomical studies of coronary sclerosis in relation to infarction of the heart. It is perhaps not beyond the role of the pathologist to record the extension of this work to correlated clinicopathological surveys. Blumgart, Schlesinger and Davis[48] have worked over from the clinical point of view the cases which Schlesinger has studied by his special technic of injection of the coronary arteries. Of particular interest are the following conclusions, with which I am heartily in accord:

> A comparative study of the clinical characteristics of coronary thrombosis and those of myocardial infarction forces the conclusion that coronary thrombosis and occlusion, per se, do not necessarily produce any characteristic clinical manifestations. . . . The syndrome usually called coronary occlusion, which consists of prolonged substernal oppression or pain, a fall in blood pressure, pallor and other manifestations of shock, and is accompanied by electrocardiographic changes, fever, leukocytosis and an increased sedimentation rate, in reality signifies myocardial infarction, and should be so termed. Anoxia, necrosis, infarction and fibrosis of the myocardium and their accompanying clinical manifestations arise whenever there is a discrepancy between the nutritional requirements of the heart muscle, on the one hand, and the factors governing nutritional supply, on the other.

Factors such as excessive exercise, attacks of congestive failure, postoperative shock and so forth may therefore bring about anoxic myocardial degeneration in the absence of severe coronary narrowing.

Another clinicopathological survey of practical importance is a study of the healing of cardiac infarcts by G. K. Mallory, White and Salcedo-Salgar.[49] A series of cases were selected in which the clinical history was adequate to date with reasonable accuracy the onset of infarction. The rate of healing was found to be inversely proportional to the size of the infarct and to the adequacy of the remaining coronary circulation. Data are recorded which should permit the pathologist to estimate with considerable accuracy the age of any infarct up to the end of the third week. To the clinician it is important to know that small infarcts are almost completely healed within a month, larger ones require six to eight weeks, and in an occasional case a central core of necrotic muscle cells encased in a heavy fibrous scar persists indefinitely. Rupture of an infarct usually occurs in the first week, occasionally in the second, very rarely beyond that period.

Venereal Lymphogranuloma

The recent review of venereal lymphogranuloma by D'Aunoy and von Haam[50] is well worth the attention of the medical profession, since it is the first comprehensive publication on the subject in the American literature, and since the authors' immense personal experience with the disease at the Charity Hospital in New Orleans permits them critically to evaluate many conflicting claims. Briefly summarized, the disease is of venereal origin and is caused by a specific filterable virus which can be grown in tissue cultures and on chorioallantoic membranes. It can be transmitted readily by intracerebral inoculations into monkeys, ferrets and mice, and irregularly by subcutaneous injection into guinea pigs, rabbits and other animals.

In men, an inconspicuous, herpetiform primary lesion is often noted on the penis. In women, it is very rarely observed. In men, enlargement of the inguinal lymph nodes is usual and is generally the symptom that brings the patient to the physician. The enlarged nodes tend to involve the skin and to break down with the formation of multiple, extremely chronic fistulous tracts. The

histologic picture of the nodes is fairly specific, with irregular "star-shaped" abscesses, bordered by a zone of epithelioid cells and occasional giant cells. Plasma cells are apt to be very numerous in the remaining nodal tissue. Not infrequently the pathologist has been the first to suggest the correct diagnosis in cases which have been submitted to biopsy.

In women the course is quite different. Presumably because of primary involvement of a deeper lymphatic chain, inguinal-node enlargement is rare. In contrast, hypertrophic or ulcerative elephantiasis of the labia or other portions of the pudenda (esthiomene) and inflammatory stricture of the rectum are the characteristic lesions. Any one of the three features or any combination can, however, occur in either sex. In contrast to the relative specificity of the histologic picture in the lymphadenitis, it is rare that anything but a nonspecific reaction is reported in esthiomene or the rectal lesions. Marked plasma-cell infiltration is somewhat suggestive.

It was the development of the Frei test that first permitted the recognition of these three widely different clinical syndromes as manifestations of a single disease. Subsequently the virus has been repeatedly recovered and identified from cases of each type. The Frei test remains our most valuable diagnostic method. Antigen prepared from infected mouse brains has proved highly specific and more readily standardizable than human antigen, despite certain claims[51] to the contrary. In competent hands a specificity and reliability approximating 95 per cent have been obtained.

Evidence is gradually accumulating that the disease does not necessarily remain localized. In the early stages generalized symptoms are frequent, and it is still uncertain to what extent they represent diffusion of the virus and to what extent they are systemic reactions to a localized infection. Of the latter type are probably the skin manifestations, both erythema multiforme and erythema nodosum, and the arthritides. Direct infection of the fallopian tubes has been reported by Schenken,[52] who has also recovered the virus from the brain of a human patient with symptoms of meningitis. Colonic lesions have been reported, and I have personally seen an isolated lesion of the sigmoid.

Certain observations of considerable interest have been recorded by Gsell.[53] In chronic cases, serum-protein determinations frequently show a significant elevation (over 9 gm. per 100 cc. in approximately half the cases), a rise caused almost wholly by elevation of the globulins. As would be expected under such circumstances, the formol-gel and Takata-Ara reactions are frequently positive. In a single bone-marrow aspiration Gsell found so many plasma cells that a diagnosis of multiple myeloma was temporarily considered.

Finally, it is becoming increasingly apparent as recognition of the disease becomes more general and the Frei test is more extensively applied that the disease is world-wide in distribution and much commoner than has generally been realized. Whether or not it is increasing cannot as yet be determined. Of its significant frequency in New England the reports of Howard and Strauss[54] and of Chapman and Hayden[55] bear witness.

Catarrhal Jaundice

Interest in catarrhal jaundice has always been great in Scandinavia. It was Flindt,[56] an obscure Danish physician, who first challenged Virchow's hypothesis of a plug of mucoid inflammatory exudate in the common duct, and offered evidence that the disease was a specific infection and that the basic lesion was a diffuse hepatic degeneration. Forgotten for thirty years, it was rediscovered by Linstedt[57] and confirmed by Wallgren.[58] Since patients with catarrhal jaundice die only in the rare event that atrophy supervenes, knowledge of the early lesions has been derived from occasional biopsies of the liver usually consequent to a mistake in clinical diagnosis. Roholm and Iversen[59] have added considerably to this by a series of thirty-eight aspiration biopsies on 26 patients, obtained at intervals from the third to the fifty-first day of the disease. In all cases they found poorly defined foci of liver-cell degeneration and necrosis, an inflammatory reaction predominantly mononuclear in character and varying proliferation of connective tissue — periportal, central and diffusely throughout the lobule. Though as a rule the hepatitis ran its course without leaving any other trace than a slight increase in connective tissue, in 3 cases the latter was marked enough to suggest cirrhosis. In 1 case, indistinguishable in its early stages from the others, a subacute atrophy developed.

A totally new suggestion as to the etiology of the disease has been offered by Andersen.[60] An epidemiological survey showed that in Denmark the incidence was lowest in Copenhagen and greatest in rural districts, particularly certain parts of Jutland where the chief economic activity is the raising of hogs. Hogs in Denmark frequently suffer from jaundice, and a fairly close parallelism was shown between the seasonal variation in the number of jaundiced hogs recorded at the slaughterhouses and the reported cases of human catarrhal jaundice. In a second paper Andersen[61] re-

ports the appearance of jaundice in young pigs a few days after feeding them bile obtained by duodenal drainage from patients with catarrhal jaundice. The experiments still await confirmation. Perhaps it will appear with poetic justice from Germany, if an epidemic of catarrhal jaundice should follow the reported confiscation of the Danish hogs.

References

1. Fahr, T.: Pathologische Anatomie des Morbus Brightii. Lubarsch and Henke's *Handbuch der speziellem pathologischen Anatomie und Histologie*. Berlin, Julius Springer, 6(1):158-473, 1925.
2. Bell, E. T., and Clawson, B. J.: Primary (essential) hypertension: study of four hundred and twenty cases. *Arch. Path.* 5:939-1002, 1928.
3. Klemperer, P., and Otani, S.: "Malignant nephrosclerosis" (Fahr). *Arch. Path.* 11:60-117, 1931.
4. Schürmann, P., and MacMahon, H. E.: Die maligne Nephrosklerose, zugleich ein Beitrag zur Frage der Bedeutung der Blutgewebsschranke. *Virchows Arch. f. path. Anat.* 291:47-218, 1933.
5. Kimmelstiel, P., and Wilson, C.: Benign and malignant hypertension and nephrosclerosis: clinical and pathological study. *Am. J. Path.* 12:45-82, 1936.
6. Goldblatt, H.; Lynch, J.; Hanzal, R. F., and Summerville, W. W.: Studies on experimental hypertension. I. The production of persistent elevation of systolic blood pressure by means of renal ischemia. *J. Exper. Med.* 59:347-379, 1934.
7. Goldblatt, H.; Gross, J., and Hanzal, R. F.: Studies on experimental hypertension. II. The effect of resection of splanchnic nerves on experimental renal hypertension. *J. Exper. Med.* 65:233-241, 1937.
8. Goldblatt, H.: Studies on experimental hypertension. III. The production of persistent hypertension in monkeys (macaque) by renal ischemia. *J. Exper. Med.* 65:671-675, 1937.
9. Keyes, J. E. L., and Goldblatt, H.: Experimental hypertension. IV. Clinical and pathologic studies of eyes. Preliminary report. *Arch. Ophth.* 17:1040-1054, 1937.
10. Goldblatt, H.: Studies on experimental hypertension. V. The pathogenesis of experimental hypertension due to renal ischemia. *Ann. Int. Med.* 11:69-103, 1937.
11. Goldblatt, H., and Wartman, W. B.: Studies on experimental hypertension. VI. Effect of section of anterior spinal nerve roots on experimental hypertension due to renal ischemia. *J. Exper. Med.* 66:527-534, 1937.
12. Goldblatt, H.: Studies on experimental hypertension. VII. The production of the malignant phase of hypertension. *J. Exper. Med.* 67:809-826, 1938.
13. Keyes, J. E. L., and Goldblatt, H.: Experimental hypertension: vascular changes in eyes. *Arch. Ophth.* 20:812-828, 1938.
14. Goldblatt, H.; Kahn, J. R., and Hanzal, R. F.: Studies on experimental hypertension. IX. The effect on blood pressure of constriction of the abdominal aorta above and below the site of origin of both main renal arteries. *J. Exper. Med.* 69:649-674, 1939.
15. Gerbi, C.; Rubenstein, B. B., and Goldblatt, H.: Studies on experimental hypertension. X. The oxygen consumption of the ischemic kidney. *J. Exper. Med.* 71:71-76, 1940.
16. Goldblatt, H.: Experimental hypertension induced by renal ischemia. *Bull. New York Acad. Med.* 14:523-553, 1938.
17. Dicker, E.: Existence de substances hypertensives dans le sang du chien pendant la compression permanente des artères rénales. *Compt. rend. Soc. de biol.* 122:476, 1936.
18. Flaut, L.: Hypertension artérielle chronique chez le chien par ischémie rénale. *Comp. rend. Soc. de biol.* 122:126, 1936.
19. Hartman, F. W.; Bolliger, A., and Doub, H. P.: Experimental nephritis produced by irradiation. *Am. J. M. Sc.* 172:487-500, 1929.
20. Page, I. H.: Production of persistent arterial hypertension by cellophane perinephritis. *J. A. M. A.* 113:2046-2048, 1939.
21. *Idem:* The relationship of the extrinsic renal nerves to the origin of experimental hypertension. *Am. J. Physiol.* 112:166-171, 1935.
22. Collins, D. A.: Hypertension from constriction of the arteries of denervated kidneys. *Am. J. Physiol.* 116:616-621, 1936.
23. Freeman, N. E., and Page, I. H.: Hypertension produced by constriction of the renal artery in sympathectomized dogs. *Am. Heart J.* 14:405-414, 1937.
24. Glenn, F.; Child, C. G., and Page, I. H.: Effect of destruction of spinal cord on hypertension artificially produced in dogs. *Am. J. Physiol.* 122:506-510, 1938.
25. Tigerstedt, R., and Bergman, P. G.: Niere und Kreislauf. *Skandinav. Arch. f. Physiol.* 8:223-271, 1898.
26. Landis, E. M.; Montgomery, H., and Sparkman, D.: The effects of pressor drugs and of saline kidney extracts on blood pressure and skin temperature. *J. Clin. Investigation* 17:189-206, 1938.
27. Williams, J. R., Jr.; Harrison, T. R., and Mason, M. F.: Observations on two different pressor substances obtained from extracts of renal tissue. *Am. J. M. Sc.* 195:339-350, 1938.
28. Corcoran, A. C., and Page, I. H.: Effects of renin, pitressin, and pitressin and atropine on renal blood flow and clearance. *Am. J. Physiol.* 126:354-367, 1939.
29. Page, I. H.: On nature of pressor action of renin. *J. Exper. Med.* 70:521-542, 1939.
30. Helmer, O. M., and Page, I. H.: Purification and some properties of renin. *J. Biol. Chem.* 127:757-763, 1939.
31. Kohlstaedt, K. G.; Page, I. H., and Helmer, O. M.: The activation of renin by blood. *Am. Heart J.* 19:92-99, 1940.
32. Page, I. H., and Helmer, O. M.: A crystalline pressor substance (angiotonin) resulting from the reaction between renin and renin-activator. *J. Exper. Med.* 71:29-42, 1940.
33. Page, I. H., and Sweet, J. E.: The effect of hypophysectomy on arterial blood pressure of dogs with experimental hypertension. *Am. J. Physiol.* 120:238-245, 1937.
34. Blalock, A., and Levy, S. E.: Studies on the etiology of renal hypertension. *Ann. Surg.* 106:826-847, 1937.
35. Page, I. H.: The effect of bilateral adrenalectomy on arterial blood pressure of dogs with experimental hypertension. *Am. J. Physiol.* 122:352-358, 1938.
36. Collins, D. A., and Wood, E. H.: Experimental renal hypertension and adrenalectomy. *Am. J. Physiol.* 123:224-232, 1938.
37. Houssay, B. A., and Fasciolo, J. C.: Secreción hipertensora del riñón isquemiado. *Rev. Soc. argent. de biol.* 13:284-294, 1937.
38. Williams, J. R., Jr., and Grossman, E. B.: The recovery of an adrenalin-like substance from the kidney. *Am. J. Physiol.* 123:364-368, 1938.
39. Collins, D. A., and Hoffbauer, F. W.: Effect of transfusion of blood from dogs with experimental renal hypertension into normal dogs. *Proc. Soc. Exper. Biol. & Med.* 35:539-541, 1937.
40. Moritz, A. R., and Oldt, M. R.: Arteriolar sclerosis in hypertensive and non-hypertensive individuals. *Am. J. Path.* 13:679-728, 1937.
41. Stewart, J. D.; Birchwood, E., and Wells, H. G.: Effect of atherosclerotic plaques on diameter of lumen of coronary arteries. *J. A. M. A.* 104:730-733, 1935.
42. Kimmelstiel, P.: Benigne Nephrosklerose und arterieller Hochdruck. *Virchows Arch. f. path. Anat.* 290:245-269, 1934.
43. Butler, A. M.: Chronic pyelonephritis and arterial hypertension. *J. Clin. Investigation* 16:889-897, 1937.
44. Barker, N. W., and Walters, W.: Hypertension associated with unilateral chronic atrophic pyelonephritis: treatment by nephrectomy. *Proc. Staff Meet., Mayo Clin.* 13:118-121, 1938.
45. Weiss, S., and Parker, F., Jr.: Pyelonephritis: its relation to vascular lesions and to arterial hypertension. *Medicine* 18:221-315, 1939.
46. Mallory, G. K.: The experimental production of healed pyelonephritis. *Arch. Path.* (in press).
47. Mallory, T. B.: Report on medical progress: pathology. *New Eng. J. Med.* 220:1037-1041, 1939.
48. Blumgart, H. L.; Schleisinger, M. J., and Davis, D.: Studies on the relation of the clinical manifestations of angina pectoris, coronary thrombosis, and myocardial infarction to the pathologic findings. *Am. Heart. J.* 19:1-91, 1940.
49. Mallory, G. K.; White, P. D., and Salcedo-Salgar, J.: The speed of healing of myocardial infarction. *Am. Heart J.* 18:647-671, 1939.
50. D'Aunoy, R., and von Haam, E.: Venereal lymphogranuloma. *Arch. Path.* 27:1032-1082, 1939.
51. Strauss, M. J., and Howard, M. E.: The Frei test for lymphogranuloma inguinale: experiences with antigens made from mouse brain. *J. A. M. A.* 106:517-520, 1936.
52. D'Aunoy, R., and Schenken, J. R.: Lymphogranuloma as cause of pelvic inflammatory disease. *J. A. M. A.* 110:799, 1938.
53. Gsell, O.: Die Bedeutung der Serumeiweiss- und Knochenmarksveränderungen bei Lymphogranuloma inguinale. *Klin. Wchnschr.* 18:778-781, 1939.
54. Howard, M. E., and Strauss, M. J.: Lymphogranuloma inguinale: report of six cases in and around New Haven. *New Eng. J. Med.* 212:323-330, 1935.
55. Chapman, E. M., and Hayden, E. P.: Lymphogranuloma inguinale; clinical study of thirty cases of sixth venereal disease in natives of New England. *New Eng. J. Med.* 217:45-57, 1937.
56. Flindt, N.: Bemaerkninger med Hensyn til den saakaldte katarralske Ikterus's Aetiologi og Genese. *Bibliot. f. laeger* S. 7, Vol. 1:420-452, 1890.
57. Linstedt, F.: Zur Kenntnis des Icterus catarrhalis und dessen Inkubationszeit. *Deutsche med. Wchnschr.* 45:434, 1919.
58. Wallgren, A.: Erfahrungen über epidemischen Icterus (sog. Icterus catarrhalis). *Acta paediat.* 9 (supp. 2):1-90, 1930.
59. Roholm, K., and Iversen, P.: Changes in the liver in acute epidemic hepatitis (catarrhal jaundice) based on 38 aspiration biopsies. *Acta Path.* 16:427-442, 1939.
60. Andersen, T. T.: Etiology of hepatitis epidemica (epidemic jaundice). *Acta med. Scandinav.* 93:209-227, 1937.
61. Andersen, T. T., and Tulinius, S.: Etiology of hepatitis epidemica (epidemic jaundice). *Acta med. Scandinav.* 95:497-509, 1938.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Antemortem and Postmortem Records as Used in Weekly Clinicopathological Exercises

founded by richard c. cabot

Tracy B. Mallory, M.D., *Editor*

CASE 26221

Presentation of Case

A twenty-two-year-old white man was admitted to the hospital complaining of pain in the neck for five months.

Approximately five months before admission the patient began noticing sharp, shooting pains in the neck, usually occurring when he stooped forward. These pains had apparently followed a gradually increasing stiffness of the neck which had progressed for two months before the pains appeared. He attributed these symptoms to a "cold" which had settled in his neck. Motion of the head and pressure over the cervical spine aggravated the discomfort. On one occasion with such movement, his neck "snapped," and he became aware of acute pain so that he was forced to remain in bed to keep the head and neck at rest. A local physician who examined him diagnosed his ailment as "arthritis." Two weeks later, because of a progression of symptoms, he was taken to an outside hospital where roentgenograms of the cervical spine were said to have shown "decay and destruction" of the cervical vertebrae. A plaster collar was applied, and he wore this constantly with complete relief of pain.

Two months before entry the right knee became painful, the pain radiating upward to the mid-thigh and perineum. The sacral and coccygeal regions, the right hip and the ilium became similarly painful a few weeks later.

Five weeks before admission he noticed beginning constipation, which progressed to obstipation so that he on one occasion failed to have a bowel movement for ten days. Anorexia, a gradual weight loss of some thirty-five pounds, and weakness continued to increase apace. For some four weeks before admission his food had consisted entirely of fluids, and apparently as a result of this large fluid intake, polyuria and nocturia appeared. Furthermore he noticed increasing nervousness, sweating and palpitation. There was no gross hematuria or passage of urinary stones. At no time had he noted redness, swelling or local heat over the painful areas of the neck, knee and pelvic regions. There were no chills, fever, headache or vomiting. Because of the obvious gravity of his illness, he was admitted to this hospital for further diagnosis and treatment.

The remaining family, marital and past histories were non-contributory.

Physical examination revealed an extremely emaciated but well-developed male who lay quietly in bed in some distress. His neck was held in a bivalved cast. On its removal nothing unusual was observed in the neck region save slight nonlocalized cervical vertebral stiffness and tenderness. The heart and lungs were normal. The blood pressure was 165 systolic, 110 diastolic. There was tenderness in the right flank and right costovertebral angle, without rigidity or palpable mass. The reflexes were depressed. There was no muscle fibrillation, but there was great generalized muscular atrophy. The remainder of the examination was negative.

The temperature, pulse and respirations were normal.

Examination of the blood showed a red-cell count of 2,680,000, with 60 per cent hemoglobin, a hematocrit reading of 30 per cent, a color index of 1.12, a mean corpuscular volume of 115 cubic microns, mean corpuscular hemoglobin of 34.2 micro-micrograms and a mean corpuscular hemoglobin concentration of 3.15 per cent. The white-cell count was 8450, with 64 per cent polymorphonuclears, 26 per cent lymphocytes, 3 per cent monocytes, 1 per cent basophils and 1 per cent eosinophils. The urine examination was negative, save that the Sulkowitch test for calciuria was positive; there was no proteinuria. The blood Hinton test was negative. The serum calcium was 18.0 mg. per 100 cc., the serum phosphorus 3.6 mg., the serum phosphatase 14.2 units and the serum protein 7.8 gm. The basal metabolic rate was + 16 per cent.

Roentgenograms of the bones of the pelvis, scapulas, mandible and visible portions of both femurs, as well as the sacrum, were riddled with defects which varied in size from half to several centimeters in diameter. Similar changes were seen in several ribs, in the first and second lumbar vertebrae and in the fourth cervical vertebra. There was a compressed fracture of the last, as well as one of the second lumbar vertebra. In several places where the disease involved flat bones—in the pubic bones and in the ribs—there was expansion of the involved bones. The bones which were not involved showed fairly normal density. The lamina dura around the teeth, so far as could be seen in the skull films, was preserved. The wing of the ilium showed particularly marked involvement and was almost completely destroyed. Further x-ray studies, including intravenous py-

elography, were either negative or not dissimilar from those previously noted.

The patient ran a slowly progressive, downhill course. On the tenth hospital day an operation was performed.

Differential Diagnosis

Dr. Wyman Richardson: I shall ask the x-ray consultant four specific questions. First, in regard to the pyelogram, is the dye concentrated sufficiently to suggest a fair renal function?

Dr. Aubrey O. Hampton: I should say that, if the patient were prepared for an intravenous pyelogram, — that is, if he were dehydrated before the dye was given, — there is something wrong with his kidneys which is probably functional. I cannot be sure of the type.

Dr. Richardson: Can you say anything about the size and shape of the kidneys?

Dr. Hampton: I cannot see the kidney outlines due to the quality of the film, but the kidney pelvis on the right side is not dilated. The left kidney pelvis is not visible.

Dr. Richardson: Is there any calcium in the kidney or calcium stones elsewhere?

Dr. Hampton: I have to take the report for that. This film was taken after the dye. Here on another film is a fairly dense kidney pelvis. Perhaps the kidney function was not so bad as I supposed on the first film. It seems to have been fairly normal, at least in one kidney.

Dr. Richardson: My last question is in regard to uninvolved bone. I should like again to have you say, — if it is so, — that the uninvolved bone is relatively normal.

Dr. Hampton: I should say that the bone between the areas of destruction is entirely normal. The numerous punched-out areas of bone destruction produce an astonishing picture particularly in a man of his age. This film provoked a lot of "ah's" in the x-ray department when left on the illuminator. It shows a very extensive, purely destructive process in the bone of a young man. The disease did extend below the elbow at this point in the radius. The skull film is not here, but the lesions there were smaller but sharp and round, similar to this. These lesions in the pelvis are unusually large.

Dr. Richardson: I am no expert on bone disease or calcium metabolism. I shall probably make many mistakes which Dr. Albright will immediately correct. I suspect this hook is baited with a choice morsel of parathyroid adenoma, but I am not biting for that. I do not see how it could be, for several reasons. In the first place, the phosphorus level is normal. Although one may get a normal or elevated phosphorus level in hyperparathyroidism, one has to presuppose then, I think, difficulty with renal function. I am going to speak of renal function later, but for the moment I shall assume that it was normal. In the second place, the phosphatase is distinctly elevated. It is my impression that, when hyperparathyroidism involves a large amount of bone, the phosphatase becomes greatly elevated. If it does not involve bone it will not be elevated at all. This process involves a tremendous amount of bone, and therefore one would expect with hyperparathyroidism an even higher phosphatase level. In the third place, it is difficult to see how a disease produced by overactivity of the parathyroid glands would produce localized lesions with normal bone elsewhere. Finally, the clinical course, which is rapidly downhill, suggests cancer rather than hyperparathyroidism, which in those cases I have seen has usually been a very much more chronic process.

Could it be secondary hyperparathyroidism? In certain cases of renal failure, there does occur, I believe, hyperplasia of the parathyroid glands. One explanation of this might be a retention of phosphorus because of damaged kidneys, with a resulting tendency to reduction of the blood calcium and an attempt on the part of the parathyroid glands to overcome this. That may be a silly explanation.

Is there any evidence of damaged renal function in this case? The patient shows clinical hypertension. The urine is reported as normal. If so, we are entitled to believe the specific gravity was above 1.020. No blood nonprotein nitrogen is reported — probably it is just as well. At least we have evidence that dye was excreted, although it may not have been excreted quite so well as normal. So on the whole it seems to me that we have very little evidence of renal failure. There may be a little. That may account for the phosphorus level as given here.

One other point — he had a macrocytic normochromic anemia. This is not uncommonly seen in uremia, but may also be seen in cancerous involvement of bone. In itself one cannot take that as evidence of renal failure. Therefore, I feel that it must be cancer. If so, what is it?

I shall rule out multiple myeloma on the basis of the patient's age. It is unusual to see myeloma in a patient this young. Otherwise it could be myeloma, it seems to me; there is no positive evidence of it, however. The serum protein was normal, and there was no Bence-Jones protein in the urine, though of course the latter does not have

to be present. No plasma cells were noted in the blood smear. Ordinary metastatic carcinoma from the thyroid gland, prostate or breast would seem very unlikely in this young man; therefore I shall rule that out. Also, the prostatic metastases to bone that I have seen have always shown a certain amount of osteoplastic activity, that is, increased density in the lesion. This lesion, as Dr. Hampton pointed out, is almost purely osteolytic.

The next problem is lymphoma. Lymphoma not infrequently involves bone, but I have never heard of such extensive involvement as this — in my experience, two or three discrete lesions are the rule.

Finally, there is the question of renal carcinoma or hypernephroma. This seems to me the most likely diagnosis. There are one or two more points to be brought out about such a diagnosis. In the first place, could widespread malignant metastases to bone produce a blood calcium of 18 mg. per 100 cc., a concentration which is very close to the lethal level? I do not know. I say it could because it apparently did. How could it? Obviously, there was a terrific destruction of bone, and I suppose the calcium had to go somewhere. Another thing we notice is that he had constipation. We might even suspect — I do not know whether this can be proved — that calcium was not being excreted in the bowel in normal fashion and could not all get out through the kidney. I do not believe that I have to assume that this patient had hyperparathyroidism, either primary or secondary, to explain the high serum calcium. However, whatever the explanation of the serum calcium, its high level seems to explain most of this patient's symptoms.

What positive evidence have we of renal carcinoma or hypernephroma? The only evidence is pain and tenderness in the right costovertebral angle and right flank. Possibly the obstipation may have had something to do with pressure in the region of the ascending colon. I think it is probably better to explain the constipation and obstipation on the basis of lack of food intake — starvation, in other words. The polyuria and polydipsia I assume are explained better as an attempt to excrete calcium than they are on any other basis. The nervousness, sweating, palpitation and muscular weakness could be due to a high blood-calcium level. Can high blood pressure be associated with it? I do not know. I might have looked up a number of these things, but I thought it would not be cricket to do that, so I have done the best I could with what I know. My diagnosis is renal carcinoma or hypernephroma.

DR. TRACY B. MALLORY: Are there any questions or comments?

DR. WILLIAM B. BREED: I think it is fair to say that everyone who saw him failed to make a diagnosis until the bone marrow was examined.

DR. BERNARD M. JACOBSON: The most important laboratory finding in ruling out multiple myeloma is the phosphatase. It does not help in the differential diagnosis, when elevated, between metastatic carcinoma and hyperparathyroidism. The last I heard about the case was that at quarter past nine this morning the pathologists were still working on the diagnosis. The sternal marrow cells, which I called "something or other which I had never seen before," resembled lymphoblasts.

CLINICAL DIAGNOSIS

Lymphoblastic lymphoma.

DR. RICHARDSON'S DIAGNOSIS

Renal carcinoma or hypernephroma, with metastases to bone.

ANATOMICAL DIAGNOSES

Lymphoblastic lymphoma.
Bronchopneumonia, slight.
Congenital anomaly — horseshoe kidney.

PATHOLOGICAL DISCUSSION

DR. MALLORY: Dr. Jacobson did a sternal puncture, and the findings were later confirmed by a sternal biopsy. In the sternal puncture he found that erythropoiesis and myelopoiesis were markedly decreased. Nearly 90 per cent of the cells present were somewhat large, round cells, with very scanty bluish cytoplasm and a nucleus which was considered consistent with that of a lymphoblast. At the end of the autopsy I have nothing to add to that. I think we must consider this a lymphoblastic type of malignant lymphoma — lymphoblastic myeloma, if one wishes to call it that. The autopsy showed very extensive destruction of the bones, with numerous spontaneous fractures, including compressed fractures of two or three vertebrae. There was virtually no involvement outside of the skeletal system that one could recognize in gross. One kidney was horseshoe shaped, so it is not surprising that the outlines were difficult to make out. Its surface showed many poorly defined, mottled, grayish areas. On microscopic examination there were multiple foci of tumor cells scattered throughout the cortex. The spleen showed small numbers of scattered tumor cells but was not significantly enlarged. The liver showed very extensive hematopoiesis, evidently compensation for the great destruction of marrow.

CASE 26222

Presentation of Case

A thirty-nine-year-old unmarried woman was admitted to the hospital complaining of pain and stiffness of the left knee.

Approximately six months before admission the patient "spontaneously" developed stiffness of the left knee. This progressed and became painful. Pain was then present constantly and was aggravated by change of position after rest. There was only slight pain during actual weight bearing, but with walking and motion, however, the joint became swollen and required the use of an Ace bandage. She found that the application of ice packs relieved the pain, but that it was markedly aggravated by heat. She was acutely aware of weather change. Gradually the knee changed in shape. The patient lost 17 pounds in weight (from 112 to 95 pounds), was anorexic and stated that everything she ate produced "gas." Throughout the illness she continued to work as a boxmaker in a factory. There were no other symptoms, save easy fatigability and a constant feeling of lassitude. One month before admission she had had an attack of dysuria, frequency and slight gross hematuria, which lasted two weeks and then cleared spontaneously. Since that time she had remained asymptomatic.

At the age of eighteen she had had a pelvic operation resulting in an artificial menopause. The remaining family and past histories were noncontributory.

Physical examination, which revealed a pale, thin, undernourished woman, was essentially negative. She walked with a slight limp, and the left knee was held in flexion at 15°. There was a slight valgus deformity of the knee. The leg, just below the joint, was definitely enlarged, forming a mass that was more noticeable laterally. The veins over the enlargement were engorged. The mass was smooth in contour, firm, and definitely warmer than were the adjacent tissues. There appeared to be slight thickening of the joint capsule with no increase in joint fluid, and the area was tender to palpation both medially and anterolaterally. The head of the fibula was normal to palpation. Measurements of the legs were within normal limits, although 2.5 cm. below the patella the left leg measured 30 cm. in circumference, and the right 28.8 cm. The motion of the left knee was limited to flexion from 15 to 120°, while the right ranged from 0 to 140°.

The temperature, pulse and respirations were normal.

Examination of the blood showed a red-cell count of 4,000,000 with a hemoglobin of 75 per cent, and a white-cell count of 6500 with 61 per cent polymorphonuclears. Examinations of the urine were negative. The serum calcium was 10.8 mg. per 100 cc., the serum phosphorus 2.5 mg., the serum phosphatase 10.3 units and the serum protein 7.6 gm. The blood Hinton and Wassermann tests were positive.

Roentgenograms of the left knee showed that the proximal 6 cm. of the left tibia close to the joint surface was markedly increased in density, the trabeculation being only incompletely visible. The increase in density was apparently produced by thickening of the cortical bone as well as by changes deeper in the bone. The bone surface was irregular in several places, without spicule formation. The appearance of the bone in these areas was more or less lacelike. No soft-tissue mass was seen, but there was some slight swelling of the soft tissues along the medial aspect of the upper portion of the tibia. This extended upward to the level of the femoral condyle. Films of the skull and chest were negative. A gastrointestinal series was negative.

On the seventh hospital day an operation was performed.

Differential Diagnosis

Dr. Roy E. Mabrey: There are a few points that I should like to mention before we see the x-ray films. The duration of the disease — six months — is not of any help in making the diagnosis. The fact that the patient lost 17 pounds in weight may have been due to the pain she had in the leg, with consequent loss of sleep and appetite. She had easy fatigability and lassitude, which again might be non-specific responses to pain and loss of weight. She had dysuria and slight gross hematuria, both of which bring up an interesting possibility. The urine itself was negative, however, at the time she was admitted. No intravenous pyelogram was done, just a flat plate of the abdomen being taken. The operation that produced an artificial menopause probably does not have any bearing on the matter. The fact that she had no increase in joint fluid would tend to indicate that this was probably not an inflammatory condition; however, that does not always hold. The white count was 6500. The other tests were normal, except for the phosphatase, which was definitely elevated. She had a gastrointestinal series, demonstrating that some interest was taken in the anorexia and the belching of gas, and the results appear to rule out any primary lesion in the stomach.

May we see the x-ray films?

DR. AUBREY O. HAMPTON: I cannot add anything to the note. The periosteal proliferation which produced the irregularity described is interesting. I know the answer so I cannot go any farther.

DR. MABREY: The problem seems to be to differentiate inflammation and a neoplasm. Acute osteomyelitis we can rule out on the duration, the absence of fever and the white count. She might have had a low-grade form, a so-called Brodie's abscess, which could last for so long a period, but in view of the extent of the lesion I think she would have had something more in the way of elevated temperature and white count. A new entity, osteoid osteoma, has been recently described. These lesions are quite small, however, and do not reach the size of this one.

The next possibility is tuberculosis. That may occur around the joints. The skin of this patient was not white, as it is in tuberculosis; the blood vessels were engorged, and the skin was warm to touch. So I feel that I can rule out tuberculosis. She had positive Hinton and Wassermann tests so we must very seriously consider syphilis. The pain in syphilis of the bone is usually nocturnal, although that is not always the case. With such a lesion we should expect a motheaten appearance; however, the lesion in this case is apparently one of a sclerosing type. The phosphatase in inflammatory lesions is usually normal, so that we have that evidence against its being syphilis.

When we come down to the neoplastic diseases there are a number we have to consider briefly. This episode of dysuria, with frequency and gross hematuria, brings up the question of whether she might have had osteitis fibrosa cystica. She could have had a parathyroid tumor with stones in the kidneys, but the laboratory tests rule it out. It is true the phosphatase was elevated, but the lesion is single and we should expect it to be multiple. We can safely rule that out. Giant-cell tumor would not give this appearance by x-ray; it is usually limited to the epiphyseal area. It is possible that it might have undergone malignant degeneration, however, and, if so, could have produced such a picture as this. This tumor does not extend up to the joint surface. You can see trabeculation of the bone up to the cartilage, which would not be true of giant-cell tumor. With that much degeneration the tumor would extend up to the cartilage and not leave any bone there. Reticulum-cell sarcoma we should not have to consider seriously. Usually the patients are older than this. Such a lesion is very extensive, without causing marked constitutional reaction. We see patients with large lesions, and yet the general condition is very good. The question of metastatic carcinoma we have to consider again, and the urinary symptoms and the finding of blood in the urine at one time might suggest a hypernephroma that had metastasized to the bone. Of course such a tumor could metastasize to any area; however, no other foci were found. The stomach was investigated, presumably because cancer of the stomach sometimes metastasizes to bone. The thyroid gland and breasts were apparently normal in this patient. The serum phosphatase may be elevated in metastatic carcinoma, although in a single lesion it is usually not increased.

Another primary tumor we have to consider is Ewing's tumor. This case has none of the characteristics — no elevation of temperature, no increase in white count and no characteristic x-ray film. As you know, with Ewing's tumor you see a lamination which gives the so-called onion-peel appearance, and there is none of that here.

We come finally to osteogenic sarcoma. The duration of the story is consistent with that of an osteogenic sarcoma. The x-ray picture is not typical because we usually consider that spicule formation is characteristic of this disease. There is involvement of both the cortex and the medulla of the bone. However, that is in favor of osteogenic sarcoma. The phosphatase is markedly increased, a finding that is consistent with osteogenic. It seems we come to three considerations: syphilis, metastatic carcinoma and osteogenic sarcoma. With the material at hand I favor osteogenic sarcoma.

DR. FULLER ALBRIGHT: There are one or two interesting points that came up. In the first place, the crux of the matter is all in the phosphatase. With syphilis you only get bone formation and bone destruction in a small area, and not a high phosphatase. A high phosphatase would rule out a small lesion, and would indicate osteogenic sarcoma or Paget's disease. Since it was not Paget's disease, I thought it was osteogenic sarcoma. I was sufficiently skeptical, however, to insist that another phosphatase be done; it turned out to be 5 units.

CLINICAL DIAGNOSIS

Bone tumor?

DR. MABREY'S DIAGNOSIS

Osteogenic sarcoma.

Anatomical Diagnosis

Bone syphilis.

Pathological Discussion

Dr. Tracy B. Mallory: As Dr. Albright has intimated, this did turn out to be syphilis. The clinical service refused to commit itself to any definite preoperative diagnosis, and the patient was operated on for biopsy. Frozen sections of the material removed at operation showed an inflammatory process, with no evidence of neoplasm, and the wound was closed after removing a few pieces of bone and of the surrounding soft tissues. In the final sections it was evident that we were dealing with a granulomatous type of infection. The predominant cell in the infiltrate was the plasma cell, and there were focal clusters of monocytes in tubercle-like groups, which are quite consistent with miliary gummas. There was absolutely no necrosis or destruction of bone, which would certainly have been present if the lesion had been tuberculous. After the histological finding and the positive serological tests I think there can be no doubt that this was a syphilitic lesion. The patient is now under antisyphilitic treatment, and says that she feels very much improved.

Dr. Hampton: In the x-ray seminar yesterday this case was shown, and I insisted that it was not osteogenic sarcoma because there was no soft-tissue mass. If an osteogenic sarcoma involves that much bone you ought to have a big tumor. The periostitis on the lateral aspect of the tibia is that of a series of blunt hills, instead of ray formation. It is a very dense and well-organized periosteal reaction, indicating a chronic process.

Dr. William B. Breed: I have been led to believe that the calcium and phosphatase determinations in this hospital are accurate and dependable. Does that hold with the phosphatase or should we be doubtful about them?

Dr. Albright: You might justifiably be doubtful about any chemical determination. The phosphatase level occasionally does jump up to 10 units for no reason. I do not know whether it is an inaccurate determination or whether something strange makes it do that.

The New England
Journal of Medicine

Formerly the
Boston Medical and Surgical Journal
Established in 1828

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND PUBLISHED UNDER THE JURISDICTION OF THE COMMITTEE ON PUBLICATIONS

Official Organ of
THE MASSACHUSETTS MEDICAL SOCIETY
THE NEW HAMPSHIRE MEDICAL SOCIETY
THE VERMONT STATE MEDICAL SOCIETY

EDITORIAL BOARD

Joseph Garland, M.D.
William B. Breed, M.D.
George R. Minot, M.D.
Frank H. Lahey, M.D.
Shields Warren, M.D.
George L. Tobey, Jr., M.D.
C. Guy Lane, M.D.
William A. Rogers, M.D.
John P. Sutherland, M.D.
Stephen Rushmore, M.D.
Hans Zinsser, M.D.
Henry R. Viets, M.D.
Robert M. Green, M.D.
Charles C. Lund, M.D.
John F. Fulton, M.D.
A. Warren Stearns, M.D.
Dwight O'Hara, M.D.

ASSOCIATE EDITORS

Thomas H. Lanman, M.D.
Donald Munro, M.D.
Henry Jackson, Jr., M.D.

Walter P. Bowers, M.D., EDITOR EMERITUS
Robert N. Nye, M.D., MANAGING EDITOR
Clara D. Davies, ASSISTANT EDITOR

SUBSCRIPTION TERMS: $6.00 per year in advance, postage paid, for the United States; Canada, $7.04 per year; $8.52 per year for all foreign countries belonging to the Postal Union.

MATERIAL for early publication should be received not later than noon on Saturday.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston, Massachusetts.

A SYMPOSIUM ON MEDICAL CARE

THE School of Law of Duke University is engaged in a program to publish a series of group magazine articles designed to inform the public about matters of public interest in its quarterly periodical, *Law and Contemporary Problems*. Two numbers in this series have been published that are of interest to the medical profession. That of January, 1939, devoted to the administration of the new food, drug and cosmetic legislation, was commented on editorially in the August 31 issue of the *Journal*. The next publication, which appeared last October, is reviewed in this issue of the *Journal*. It includes fourteen articles by prominent lawyers, investigators and students of legislative procedures pertaining to public health, medical practices and the proposed insurance plans relating thereto which have been under consideration by state legislatures and Congress.

In these articles, especial emphasis is placed on two major trends in the field of medical care. The first consists of a discussion of the development of corporations and associations, sponsored either by medical organizations, by consumer groups or by governmental agencies, all "organized to provide hospital service and medical care on a prepayment basis." The second deals with the principles underlying the administration of the plans for grants-in-aid of federal funds to extend state health plans, with particular consideration of the Wagner Bill, not so much, however, in advocacy of the proposals but rather to clarify in the minds of the people the composition and functions of these several agencies now being devised for adoption or which may be created later. Although voluminous articles and discussions have been put before the public covering the attitude of the governmental agencies and the plans now in operation or under consideration by state, county and group medical organizations, there is, probably, a considerable proportion of the medical and lay public that has a vague or incomplete knowledge of the complicated problems involved; hence an evaluation of these articles by open-minded students of these subjects is helpful in developing practical solutions of the controversial propositions. Undoubtedly the School of Law of Duke University is engaged in a worthy effort to present evidential facts and the bearing of them on matters of importance before the citizens of this country.

At the present time the nation is being importuned by students of health problems to reconstruct its attitude and procedures relating to the prevention and treatment of disease. With this purpose in view, legislation is being devised in a program centered in the Wagner Bill or its successor, now before Congress, and it is pertinent that a non-medical body representing a sister profession should present the results of its study of the situation and the proposed measures to be incorporated in this bill.

Most of the articles in the symposium have a

bearing on those sections of the bill and its associated provisions relating to health, and study of these papers will aid in the drafting of the indicated legislation. It is therefore appropriate that the medical profession and the public should unite in the expression of appreciation of the work of the authors of these papers.

THE RISK OF BIOPSY

One of the deterrents to early and accurate diagnosis of malignant tumors has been the fear, more or less unwarranted, that biopsy might lead to dissemination of the neoplastic cells. On the basis of clinical experience, however, the advantages of accurate knowledge of the nature of a tumor far outweigh theoretical dangers of metastasis. In addition, some data based on observations on animal tumors are available. A curious commentary on our occasionally illogical thought is provided by those who unhesitatingly curette a uterine neoplasm and yet balk at biopsy of a breast tumor.

From any aspect it is better when possible to excise a tumor nodule intact and thus avoid the potential spreading of tumor cells. When this is not possible, various means of obtaining tissue have been proposed, such as aspiration biopsy. Aspiration biopsy is not so favorable for diagnosis as methods giving more adequate tissue, but is relatively simple.

The dangers of incisional biopsy have probably been exaggerated. A recent important contribution on this subject has been made by Paterson and Nuttall,* who followed a group of patients with epidermoid carcinomas of the skin and mucous membranes of the mouth which were treated by radiation. Early lesions, without clinical evidence of involvement of the lymph nodes, had biopsy specimens removed by sharp ring forceps; no electrocoagulation was used, and the portions of tissue removed were large. All cases were treated essentially alike and seen in the regular follow-up clinic of the hospital; 202 cases were initially included in the study but certain ones were discarded because they did not entirely meet the criteria. Finally 99 cases with biopsy and 67 cases without biopsy were studied from the standpoint of metastasis; 19 per cent of the biopsied cases showed metastasis, and 20 per cent of the non-biopsied cases.

This careful piece of work demonstrates that in carcinoma of the skin and mucous membranes biopsy does not increase the likelihood of metastasis. It is probable that a similar study of carcinomas of the breast or of the rectum would have a similar result.

*Paterson, R., and Nuttall, J. R.: An evaluation of the risk of biopsy in squamous carcinoma. *Am. J. Cancer* 37:64-68, 1939.

MEDICAL EPONYM

Buck's Extension

The extension apparatus which bears Gurdon Buck's (1807–1877) name was first described by him before the New York Academy of Medicine at a meeting held on March 20, 1861. A report of the paper was given by Dr. George F. Shrady in the *Bulletin of the New York Academy of Medicine* (1: 181–188, 1861):

> A roller bandage is commenced at the toes in the usual way, and continued to the ankles, where it is temporarily arrested. A band of adhesive plaster two and a half to three inches broad, and long enough to allow the middle of it to form a loop below the sole of the foot, and the ends to extend above the condyles of the femur, is then applied on either side, in immediate contact with the limb, from the ankle upwards. Over this the bandage is continued as high up as the plaster. A thin block of wood of the width of the plaster, and long enough to prevent pressure over the ankle, is inserted into the loop, and serves for the attachment of the extending cord, which is fastened to an elastic rubber band (such as is used for door springs), that passes round the block. . . . The limb is now prepared to be put under extension. . . . A strip of inch board three inches wide is fastened upright to the foot of the bedstead, and perforated at the height of four or five inches above the level of the mattress. Through this hole the extending cord is to be passed, and on the further side of the strap a screw pulley should be inserted at the proper level over which the cord, with the weight attached, is to play. . . . Coaptation splints . . . should be secured . . . by . . . elastic bands. . . . Counterextension must be maintained by the usual perineum band lengthened out in the direction of the long axis of the body, and fastened to the head of the bedstead.

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

SECTION OF OBSTETRICS AND GYNECOLOGY*

RAYMOND S. TITUS, M.D., *Secretary*
330 Dartmouth Street
Boston

PYELITIS OF PREGNANCY

Mrs. C. C., a thirty-eight-year-old primipara, four months pregnant, was admitted to the hospital on September 6, 1935, with chills, fever, malaise, nausea and vomiting. She gave a history of having had these symptoms for two months.

The family history was negative. The patient's past history was essentially negative. Catamenia began at thirteen, were regular with a twenty-eight-day cycle, and lasted five days. The last period was April 20, making the expected date of delivery January 27, 1936.

Physical examination showed a well-developed and well-nourished woman. The heart was not enlarged; there were no murmurs. The lungs were clear and resonant; there were no rales. The uterus was enlarged to a size consistent with the period of amenorrhea, and a uterine fibroid was evident on palpation. The urinary sediment showed large numbers of white blood cells in clumps; there were no red cells and no casts. A urine culture showed *Bacillus coli*. Blood examination showed the hemoglobin to be 80 per cent, the red-cell count 3,870,000, and the white-cell count 8600. A blood culture taken on September 7 showed *Staphylococcus albus*.

On September 9 the hemoglobin was 80 per cent, the red-cell count 3,800,000, and the white-cell count 10,500. She was transfused with 300 cc. of citrated blood.

The temperature rose steadily until it reached a peak of 103.6°F. on the fifth day, then gradually dropped until it reached normal on the tenth day.

On September 15 the patient was cystoscoped. The infected right renal pelvis was irrigated with boric acid solution, the catheter being left in place for twenty-four hours. The patient was discharged on September 29, asymptomatic.

The patient was carried to term with some difficulty, her general health being poor. She was admitted to the hospital at term on January 27, 1936. At that time her urine still showed many white cells but there were no definite kidney complaints. The delivery was uneventful, as was the postpartum course.

Comment. This case illustrates the modern treatment of pyelitis with kidney lavage and with catheter drainage for twenty-four hours, cultures of the blood and urine having been taken. Transfusions in small amounts are often very beneficial to patients who become run-down and anemic from pyelitis, and the small transfusion in this case was done for its tonic effect rather than because of severe anemia as at the time the hemoglobin was 80 per cent and the red-cell count almost 4,000,000. No subsequent attack of pyelitis occurred before delivery.

*A series of selected case histories by members of the section will be published weekly. Comments and questions by subscribers are solicited and will be discussed by members of the section.

DEATHS

HARDING — GEORGE F. HARDING, M.D., of Brookline, died May 16. He was in his seventy-ninth year.

Born in Dorchester, he attended Harvard University and received his degree from Harvard Medical School in 1889. He was a member of the Massachusetts Medical Society and the American Medical Association.

His widow, two sisters and a brother, survive him.

KENNELLY — JULIA G. KENNELLY, M.D., of Cambridge, died February 9. She was in her seventy-second year.

Dr. Kennelly received her degree from the Woman's Medical College of Pennsylvania in 1900. She was a former member of the Massachusetts Medical Society, and had retired from active practice.

SHATTUCK — ALBERT M. SHATTUCK, M.D., of Worcester, died May 26. He was in his seventy-first year.

Born in Groton, he received his degree from the Dartmouth Medical School in 1895. He was on the staff of the Worcester City Hospital and the Memorial Hospital, Worcester, for many years. Dr. Shattuck was a fellow of the Massachusetts Medical Society and the American Medical Association.

His widow and a son survive him.

STILES — FRED M. STILES, M.D., of Waltham, died recently. He was in his seventy-seventh year.

Born in Westbrook, Maine, he received his degree from Bowdoin Medical School in 1890 and did postgraduate work at Harvard Medical School.

Dr. Stiles was a member of the Massachusetts Medical Society and the American Medical Association.

His daughter survives him.

SWEENEY — JOHN G. SWEENEY, M.D., of Hingham, died May 16. He was in his forty-sixth year.

He received his degree from Tufts College Medical School in 1916. Dr. Sweeney was former medical examiner for the Plymouth District and a former member of the Massachusetts Medical Society.

MISCELLANY

NEW CHARITY TO CORRECT SPEECH DEFECTS

A Massachusetts charter has just been granted the Institute for Speech Correction, Incorporated, organized without capital stock, to give the most up-to-date instruction in overcoming stammering, lisping and other speech defects exactly at cost. This new corporation has taken

over the Boston Stammerers' Institute, which was the oldest school of its kind in America.

Arrangements have been made with Emerson College whereby adequately supervised advanced students in speech pathology will instruct without charge any pupil at the institute who, on recommendation of his family physician, cannot pay for his lessons.

The following public-spirited educators, psychiatrists and business men have been elected trustees and are giving their services without compensation: Harry S. Ross, president of Emerson College; Frederick C. Packard, Jr., associate professor of public speaking, Harvard University; Dr. Edgar C. Yerbury, director of the Division of Mental Hygiene, Massachusetts Department of Mental Health; Joel W. Eastman, attorney; John M. Taylor, banker; Seth T. Gano, bank director and trustee; Dr. Douglas A. Thom, professor of psychiatry, Tufts College Medical School; and Payson Smith, LL.D., lecturer at Harvard University Graduate School of Education.

Samuel D. Robbins, permanent secretary of the American Speech Correction Association and professor of psychology at Emerson College, has been elected managing trustee. Mr. Robbins was for twenty-five years director of the Boston Stammerers' Institute, which was founded in 1867.

RÉSUMÉ OF COMMUNICABLE DISEASES IN MASSACHUSETTS FOR MARCH, 1940

Diseases	March 1940	March 1939	Five-Year Average*
Anterior poliomyelitis	1	0	0
Chickenpox	1471	1181	1376
Diphtheria	9	14	19
Dog bite	732	754	738
Dysentery, bacillary	36	24	6
German measles	56	105	1248
Gonorrhea	308	384	461
Lobar pneumonia	609	900	723
Measles	1487	4290	3034
Meningococcus meningitis	3	5	19
Mumps	866	1015	1260
Paratyphoid B fever	11	1	2
Scarlet fever	607	895	1233
Syphilis	501	416	551
Tuberculosis, pulmonary	242	315	296
Tuberculosis, other forms	20	28	38
Typhoid fever	3	4	5
Undulant fever	5	3	3
Whooping cough	644	970	946

*Based on figures for preceding five years.

RARE DISEASES

Anterior poliomyelitis was reported from: Boston, 1; total, 1.

Diphtheria was reported from: Abington, 1; Boston, 3; Chelsea, 1; Fall River, 1; Monson, 1; Waltham, 1; Wrentham, 1; total, 9.

Dysentery, bacillary, was reported from: Amherst, 2; Attleboro, 1; Belchertown, 24; Beverly, 1; Boston, 1; Malden, 1; Marblehead, 1; Northampton, 1; Norwood, 1; Sterling, 3; total, 36.

Infectious encephalitis was reported from: Melrose, 1; Webster, 1; total, 2.

Leprosy was reported from: Medford, 1; total, 1.

Meningococcus meningitis was reported from: Chelsea, 1; Hadley, 1; Wilmington, 1; total, 3.

Paratyphoid B fever was reported from: Arlington, 1; Boston, 1; Brookline, 2; Marblehead, 1; Milton, 1; Revere, 2; Salem, 1; Wakefield, 1; Worcester, 1; total, 11.

Pfeiffer bacillus meningitis was reported from: Dracut, 1; Millis, 1; total, 2.

Septic sore throat was reported from: Boston, 10; Boxford, 3; Cambridge, 6; Fall River, 3; Lexington, 1; Malden, 1; Medford, 3; New Bedford, 1; Sturbridge, 2; Watertown, 1; Webster, 1; Whitman, 1; total, 33.

Tetanus was reported from: Boston, 1; total, 1.

Trachoma was reported from: Boston, 2; total, 2.

Trichinosis was reported from: Boston, 1; Lynn, 3; total, 4.

Typhoid fever was reported from: Lynn, 1; North Andover, 1; Somerville, 1; total, 3.

Undulant fever was reported from: Boston, 1; Greenfield, 1; Springfield, 1; Wayland, 1; Williamstown, 1; total, 5.

The reported incidences of chickenpox and undulant fever were slightly above the five-year averages.

Paratyphoid B fever had its highest March incidence since 1934.

Bacillary dysentery, primarily of the Sonne type, continues to be prevalent, although at a slightly lower level than that of last month.

Diphtheria, German measles, measles, mumps and lobar pneumonia were reported well within the five-year averages.

The reported incidences of anterior poliomyelitis, dog bite, gonorrhea, syphilis and whooping cough were at expected levels.

There was nothing remarkable in the reported incidences of tuberculosis, typhoid fever and scarlet fever.

NOTES

The appointment of Dr. Walter L. Mendenhall, professor of pharmacology at Boston University School of Medicine, to the revisory board of the *United States Pharmacopoeia* was recently announced.

The appointment of Dr. William T. Green as director of the After-Care Clinic of the Harvard Infantile Paralysis Commission was recently announced at Harvard University. He was appointed assistant professor of orthopedic surgery this spring at Harvard Medical School, and since 1934 has been a member of the staff of Harvard Medical School and of the Children's Hospital, Boston.

The members of the commission are Dr. John E. Gordon, chairman, and Drs. Kenneth D. Blackfan, C. Sidney Burwell, Cecil K. Drinker, Frank R. Ober, Alton S. Pope, George B. Wislocki and Hans Zinsser.

REPORTS OF MEETINGS

HARVARD MEDICAL SOCIETY

A regular meeting of the Harvard Medical Society was held at the Peter Bent Brigham Hospital on February 13, with Dr. Elliott C. Cutler presiding.

The first case presented was that of a forty-one-year-old man who entered the hospital complaining of progressive weakness and pains shooting down the backs of both legs. One year prior to admission he had successfully passed an insurance examination. One month before entry he had noted a slight upper-respiratory infection, and this was followed by a typical attack of lobar pneumonia with hemoptysis and a temperature of 103°F., successfully treated with sulfapyridine. He never seemed to recover and began noting weakness and shooting leg pains. Physical examination was negative except for tenderness of the left hip and both gastrocnemii and pain on flexion of the left hip. Routine laboratory studies were normal. A flat plate of the abdomen revealed destructive lesions in the

bony pelvis and lumbar spine, and subsequent roentgenograms showed a lesion diagnosed as primary carcinoma of the lung. Pain was essentially unrelieved by x-ray therapy.

In discussing the case Dr. Merrill C. Sosman reminded the audience of the frequency with which pulmonary carcinoma has its first manifestations in its metastases and is ushered in by one or more attacks of pneumonia.

The surgical case was that of a thirty-nine-year-old man who was brought to the hospital in a semicomatose state after allegedly being struck and injured by an automobile. The patient entered with multiple contusions and abrasions. The temperature was 101°F., the pulse 140, and the respirations 20. He was found by x-ray study to have a compound, comminuted fracture of the left lower leg which was debrided under spinal anesthesia. Gas-bacillus antitoxin was administered. Lumbar puncture revealed a bloody fluid, but the patient was not subjected to x-ray studies of the skull. His course in the hospital was one of gradual mental clearing and general improvement. Dr. Cutler congratulated the house staff on refraining from taking x-ray films of the skull, for he considered the condition of the brain more important than that of its casing. He also reminded the audience that accidents in the home are the only ones more frequent than those caused by the ubiquitous automobile.

The speaker of the evening was Dr. Alan R. Moritz, professor of legal medicine at the Harvard Medical School, whose subject was "The Application of Medical Science to the Administration of Justice." He pointed out that despite the existence in European universities of departments of legal medicine for fifty to one hundred years, the recent establishment of such a unit at Harvard Medical School was the first of its kind on this continent. Dr. Moritz criticized our coroner system, inherited from England, because of the uncertain political tenure of the coroner, who is not even required to have professional qualifications. A non-political medical examiner's system is much better.

To emphasize the importance of a qualified professional physician as medical examiner, Dr. Moritz referred to typical incidents where competent judgment was necessary. In regard to homicide, the time of death may be important, even if only approximate; this can be estimated in numerous ways. The circumstances of death may be ascertained by the configuration of fracture lines, by the path of a bullet or by the gastric contents.

An interesting study in New York City has shown that 40 per cent of adult pedestrians killed by automobiles were under the influence of alcohol. This was considered important collateral information in placing blame in such cases. The same investigation revealed that almost 50 per cent of fatal assaults occurred in persons whose alcoholic content in the brain was at such a level that it was likely to predispose to quarreling; frequently knowledge of this character constituted valuable evidence in assessing the degree of guilt of an accused person.

Dr. Moritz stressed the importance of investigating cases of sudden death even though there is no evidence of unnatural causation. Many such cases are found at autopsy to have resulted from unsuspected physical or chemical injuries. Similarly, the finding of numerous cases of poisoning recently in Philadelphia and Cincinnati has confirmed the feeling that an untold number of such unsuspected unnatural deaths probably occur in this country and pass unnoticed in those communities not supplied with a competent medical-examiner system.

Another phase of death wherein such a system clarifies matters is that which concerns those who die of natural causes but with external signs of violence. Dr. Moritz alluded to the fact that there are many people walking about, driving cars and frequenting places where unexpected collapse is almost sure to result in violent injury. The latter has often been the death-certificate diagnosis when there was either no autopsy or only a superficial one, whereas the true cause of death might well have been a coronary thrombosis. The speaker cited as an illustration the unfortunate husband who was sentenced to prison for homicide because he slapped his wife's face shortly before she was stricken with a cerebral embolus arising from a diseased heart. Actually about five of every one hundred deaths, thought clinically to be due to violence, are found at autopsy to have resulted from natural causes.

Dr. Moritz also referred to the great loss to vital statistics each year because of incomplete investigation of cases of sudden or unexpected death. Many deaths from diseases such as tuberculosis, syphilis, poliomyelitis, meningitis, pneumonia, and so forth, escape recognition.

Methods at the disposal of the scientific investigator of crime were discussed briefly by the speaker. Among the important chemical studies are the recognition of alcohol in the tissues and the diverse methods of running down "story-book" clues. The latter were held to be of practical importance in many cases. Microscopy also plays a role in this regard, but Dr. Moritz suggested that it is probably more important to know where to get expert assistance than it is to attempt to maintain a complete consulting staff in each laboratory.

In regard to the problem of medical testimony in court the speaker warned of the dangers of expecting a judge or jury to be able to choose competently between the testimony of partisan rivals in psychiatric cases. He advocated instead the appointment by the court of a nonpartisan medical expert for all such problems. Dr. Moritz also criticized a too strict adherence to the doctrine of protection against self-incrimination. By improperly employing this defense, a lawyer may refuse to allow routine physical examination or urinalysis, as well as more elaborate tests on clothing, hair, and so forth, of his client.

NOTICES

ANNOUNCEMENT

THOMAS J. CAVANAUGH, M.D., announces the opening of an office at 270 Commonwealth Avenue, Boston.

REMOVAL

H. S. QUEEN, M.D., announces the removal of his office to Hotel Brandon Hall, 1501 Beacon Street, Brookline.

NEW ENGLAND HEALTH EDUCATION ASSOCIATION

The annual conference of the New England Health Education Association will be held Friday and Saturday, June 7 and 8, at the Massachusetts Institute of Technology in Cambridge.

The conference will open Friday afternoon with inspection of the exhibits and a social hour, followed by the annual business meeting at 5:30 p.m. The guest speaker at the dinner (6:30 p.m.) will be Helen S. Mitchell, Ph.D., research professor of nutrition at the Massachusetts State College in Amherst. Her subject will be, "Food Facts and Fallacies."

On Saturday morning, Samuel Prescott, Ph.D., will give the address of welcome. Henry Otto, Ph.D., consultant

in education of the W. K. Kellogg Foundation, Battle Creek, Michigan, will speak on "Health Education and Its Relation to Public Health and Medical Care." Other speakers will be Miss Helen Almy, director of social service at the Massachusetts Eye and Ear Infirmary, who will speak on "A Medical-Social Approach to a National Health Program," and Dr. Allan M. Butler, of Boston, who will speak on "The Need for Conservatism in the Provision of Budgeted Medical Services."

The conference will close with a luncheon. Miss Mabel C. Bragg, Boston University, will be the speaker. Miss Mabel M. Brown, president of the association, will preside.

HARVARD MEDICAL ALUMNI ASSOCIATION

The annual meeting and dinner of the Harvard Medical Alumni Association will take place on Wednesday, June 12, at 7:15 p.m. at the Harvard Club of New York during the annual session of the American Medical Association. The speakers will be President James B. Conant and Drs. C. Sidney Burwell, Lincoln Davis and Cornelius P. Rhoads.

NEW ENGLAND HOSPITAL FOR WOMEN AND CHILDREN

The monthly clinical conference and meeting of the staff of the New England Hospital for Women and Children will be held in the classroom of the nurses' residence on Thursday evening, June 6, at 7:15 p.m. The program will consist of case presentations of cardiac disease, maternity deaths and diarrhea with the autopsy results.

1940 GRADUATE FORTNIGHT

The 1940 Graduate Fortnight of the New York Academy of Medicine will be held from October 14 to 25. The purpose of this meeting is to make a complete study and authoritative presentation of a subject of outstanding importance in the practice of medicine and surgery. The current topic is "Infections."

There will be a carefully integrated program, which will include morning panel discussions, afternoon clinics and clinical demonstrations at many of the hospitals of New York City, evening addresses and appropriate exhibits. The evening sessions of the Academy will be addressed by recognized authorities in their special fields, drawn from leading medical centers of the United States. The comprehensive exhibit will include books and roentgenograms, pathologic and research material, and clinical and laboratory diagnostic and therapeutic methods. It is also planned to provide demonstrations of exhibits.

The following subjects will be included: experimental basis of chemotherapy in the treatment of bacterial infections; clinical bacterial chemotherapy, results obtained and dangers encountered; a general consideration of bacterial infections; recent advances in knowledge of streptococcal infections; infections of the mouth, pharynx and upper respiratory tract; infections of the middle ear and nasal sinuses; infections of the teeth and surrounding structures; influenza; pneumococcal infections; bacterial meningitis; infections of the urinary tract; gonococcal infections in the male; gonococcal infections in the female; osteomyelitis and pyogenic infections of the joints; wound infections; puerperal infections; treatment of infections by methods other than chemotherapy; virus infections; acute poliomyelitis; brucellosis — undulant fever; rickettsial diseases; lymphogranuloma venereum; epidemic encephalitis; other forms of encephalitis and choriomeningitis; and exanthematous diseases.

The Academy provides this program for the fundamental purpose of medical education, consequently all members of the medical profession are eligible for registration. A complete program and registration blank may be secured by addressing: Dr. Mahlon Ashford, New York Academy of Medicine, 2 East 103d Street, New York City.

CHILDREN'S MEMORIAL HOSPITAL, MONTREAL

The Annual Postgraduate Course which has been given for the past three years at the Children's Memorial Hospital, Montreal, will not be held this year. It is not the intention of the hospital to discontinue the course, but rather to postpone it, due to the war and to an extensive building program. As soon as conditions permit, the course will be resumed with improved facilities.

SOCIETY MEETINGS AND CONFERENCES

Calendar of Boston District for the Week Beginning Sunday, June 2

Thursday, June 6

7:15 p.m. Clinical conference and meeting of staff. New England Hospital for Women and Children.

Friday, June 7

New England Health Education Association. Massachusetts Institute of Technology, Cambridge.

Saturday, June 8

New England Health Education Association. Massachusetts Institute of Technology, Cambridge.

June 4–6 — National Gastroenterological Association. Page 737, issue of April 25.

June 4–7 — American Association of Industrial Physicians and Surgeons. Page 654, issue of April 11.

June 7, 8 — American Heart Association. Page 469, issue of March 14.

June 7–10 — American Board of Obstetrics and Gynecology. Page 608, issue of April 4.

June 8 — Dedication of Osler Memorial. Page 862, issue of May 16.

June 8 and 10 — American Board of Ophthalmology. Page 719, issue of November 2.

June 8–10 — American College of Chest Physicians. Page 781, issue of May 2.

June 10 — American Medical Golfing Association. Page 824, issue of May 9.

June 10, 11 — American Neisserian Medical Society. Page 898, issue of May 23.

June 10–14 — American Medical Association. Annual meeting, New York City.

June 10–14 — American Physicians' Art Association. Page 332, issue of February 22.

June 12 — Harvard Medical Alumni Association. Notice above.

June 12 — New England Obstetrical and Gynecological Society. Page 898, issue of May 23.

June 12 — Jefferson Medical College Alumni Association. Page 898, issue of May 23.

June 23–25 — Maine Medical Association. Annual meeting. Rangeley Lakes.

June 25–27 — Medical Library Association. Page 862, issue of May 16.

June 27 — Pentucket Association of Physicians. The Try-Angle, Groveland.

September 2–6 — American Congress of Physical Therapy. Page 862, issue of May 16.

October 8–11 — American Public Health Association. Page 655, issue of April 11.

October 11, 12 — Pan-American Congress of Ophthalmology. Page 898, issue of May 23.

October 14–25 — 1940 Graduate Fortnight of the New York Academy of Medicine. Notice above.

October 21 — American Board of Internal Medicine, Inc. Page 369, issue of February 29.

District Medical Society

MIDDLESEX NORTH

July 31.

October 30.

BOOKS RECEIVED FOR REVIEW

The Early Diagnosis of the Acute Abdomen. Zachary Cope. Eighth edition. 257 pp. London and New York: Oxford University Press, 1940. $3.75.

A Text-Book of Psychiatry for Students and Practitioners. D. K. Henderson and R. D. Gillespie. Fifth edition. 660 pp. London and New York: Oxford University Press, 1940. $6.00.

Immune-Blood Therapy of Tuberculosis: With special references to latent and masked tuberculosis. Joseph Hollós. 197 pp. Boston: Bruce Humphries, Inc., 1938. $2.50.

Psychiatric Clinics for Children: With special reference to state programs. Helen L. Witmer. 437 pp. New York: The Commonwealth Fund, 1940. $2.50.

Clinical Parasitology. Charles F. Craig and Ernest C. Faust. Second edition. 772 pp. Philadelphia: Lea & Febiger, 1940. $8.50.

Diagnosis and Treatment of Head Injuries. Sidney W. Gross and William Ehrlich. 275 pp. New York: Paul B. Hoeber, Inc., 1940. $5.00.

Minor Surgery. Frederick Christopher. Fourth edition. 990 pp. Philadelphia and London: W. B. Saunders Co., 1940. $10.00.

The Compleat Pediatrician: Practical, diagnostic, therapeutic preventive pediatrics. Wilburt C. Davison. Third edition. 256 pp. Durham: Duke University Press, 1940. $3.75.

Electrocardiography. Chauncey C. Maher and Paul H. Wosika. Third edition. 334 pp. Baltimore: Williams & Wilkins Co., 1940. $4.00.

Obesity and Leanness. Hugo R. Rony. 300 pp. Philadelphia: Lea & Febiger, 1940. $3.75.

The Foot and Ankle: Their injuries, diseases, deformities and disabilities. Philip Lewin. 620 pp. Philadelphia: Lea & Febiger, 1940. $9.00.

A Manual of the Common Contagious Diseases. Philip M. Stimson. Third edition. 465 pp. Philadelphia: Lea & Febiger, 1940. $4.00.

BOOK REVIEWS

Medical Care. Vol. VI, No. 4. *Law and Contemporary Problems.* 182 pp. Durham, North Carolina: Duke University School of Law, 1939. 75 cents.

This volume, the Autumn, 1939 issue of *Law and Contemporary Problems,* contains fourteen articles, contributed by men all holding scientific or professional degrees. Each of these contributions is worthy of elaborate analysis, but space is not available for more than a discursive review with the hope that sufficient interest will be aroused for their more detailed study.

The first article, by I. S. Falk, member of the Interdepartmental Technical Committee on Medical Care, gives the historical background of the awakened and progressive interest in the socioeconomic proposals set forth in the subsequent chapters. His contribution is an informative and logical disquisition concerning the facts and experiences which have influenced earlier workers in the fields of public health and economics pertaining to medicine.

The second, by Martin W. Brown, general secretary, Bureau of Co-operative Medicine, carries the theme of the first through the history of some experimental organizations. He describes the economic and varying problems of medical care which have arisen because of the advances in the application of scientific knowledge, the development of medical institutions and the growth of specialties leading to the operation of eight groups engaged in furnishing medical care, thereby showing the differences in the fundamentals that prevail in the experiments which have been made to determine the success of such organizations.

Joseph Laufer, editor-in-chief of the *Duke Bar Association Journal,* in the third article discusses that type of medical care which is classified as contract practice and which includes the intermediate offices of a third party, individual or organization, who or which contracts with physicians individually or collectively for service to a group of patients. He includes a history of group and contract practice and of the operation of these organizations, which, in certain instances, ran counter to the ethical principles adopted by the American Medical Association.

The fourth article under the caption "Enabling Legislation for Non-Profit Hospital Service Plans" is by C. Rufus Rorem, the director of the Commission on Hospital Service of the American Hospital Association. After showing that hospitalization is one of the unpredictable and expensive forms of health service which together with other incidental expenses constitutes an economic hazard that can be logically avoided by resort to insurance, the author explains the attitude of the states in dealing with the problems raised by insurance methods, to spread the costs of medical care. This has required the study of state laws which vary widely, as shown in decisions by state insurance departments where the ruling has been that hospital-service insurance necessitates special enabling acts. That this plan for enabling acts is not a simple solution of the problem is shown by the many essential details of administration.

Maurice J. Norby, research director of the Council on Hospital Service Plans of the American Hospital Association, continues the discussion of hospital-service plans, including their contract provisions and administrative procedures, in the fifth article. He describes hospital service as a form of protection which means collective co-operation in the equalization of losses resulting from the uncertainty of health, but states that it is not health insurance since it provides for only one form of health service through a corporation. He then proceeds to define the different forms of contracts and the subscriber's relations thereto. In this scheme, group enrollment is essential for apparent reasons. This article is a continuation and amplification of the facts and theories and the details of operation set forth in the preceding chapter, and should be studied with the other.

The sixth article, presented by William J. Burns, executive secretary of the Michigan State Medical Society, deals with the medical-service problems of Michigan, culminating in the passage of the first group-medical-care enabling act on the statute books of a large industrial state, which was the result of the combined efforts of the state government, the state medical society and the state department of insurance. Payments for the benefits provided in the act include private corporations, association groups, individuals and the governmental agencies (in behalf of indigents). Each contract is with the subscriber patient so that no third party comes between the patient and physicians. This act has served in many particulars as a model for others.

Another illustration of a non-profit medical-service corporation is presented by Hartley F. Peart, president of the Bar Association of San Francisco, and Howard Hassard, member of the California Bar, in the seventh chapter. The managerial functions in this plan are carried by a board of trustees and the service is conducted by California physicians who are paid by the so-called unit system, which distributes the accumulated pool funds among the participating physicians. Full beneficiary memberships are applicable to those whose family incomes do not exceed $3000 a year, but families in the higher brackets are eligible for benefits on payment of additional fees to the doctor.

The eighth article is under the title of "The Medical-Care Program for Farm-Security-Administration Borrowers," by R. C. Williams, who began his career as a practitioner of medicine and after three years entered public-health service and now is chief medical officer of the Farm Security Administration, and deals with 100,000 low-income farm families that are borrowers from this administration. The service became necessary because of the economic distress of 3,000,000 farm families in more than twenty states. The illness problem of this large group, which is both a cause and a result of poverty, involved the necessity of devising plans which would ensure medical care at rates bearing relation to the financial situation and the co-operation of physicians in the adjustment of fees. State medical associations co-operated in the plans adopted in conformity with principles promulgated by the American Medical Association. All the administrative details are set forth in this article and cover the various forms of service.

The ninth chapter deals with the "Anti-Trust Prosecutions against the American Medical Association," contributed by Benjamin D. Raub, Jr., the current-decisions editor of the *Duke Bar Association Journal*. This article gives a description of the organization of the Group Health Association, Incorporated, of Washington, District of Columbia, a non-profit co-operative organization for the purpose of furnishing medical care and hospitalization to its members and their dependents on a risk-sharing prepayment basis. It is a voluntary association with membership originally limited to employees of the Home Owners' Loan Corporation, with the further explanation that the only connection between the federal government and the Group Health Association was a grant of $40,000 by the Home Owners' Loan Corporation, made because of the opinion that the Group Health Association would reduce the loss of employees' services through illness. Congress discussed the propriety of this grant but took no action. Later the Group Health Association voted to include as eligible for membership all civilian employees of the executive branch of the government and voted to assess themselves to create a fund for repayment of the grant of the Home Owners' Loan Corporation.

The Medical Society of the District of Columbia initiated a policy of opposition to the Group Health Association. The legality of the association was questioned in suits brought by the insurance commissioner of the District of Columbia on the ground that it was engaged in the insurance business and by the United States district attorney on the ground that it was a corporation engaged in the practice of medicine. The court held that neither of these allegations was correct. Then followed suits against the American Medical Association, the Medical Society of the District of Columbia, the Harris County Medical Society of Texas and certain individuals for alleged violation of Section 3 of the Sherman Act, which declares it a misdemeanor to "engage in any . . . combination or conspiracy . . . in restraint of trade in . . . the District of Columbia."

A summary of the indictment is to the effect that the defendants conspired to restrain the Group Health Association in its business of arranging for the provision of medical care and hospitalization to its members and their dependents, to restrain its members in obtaining by co-operative efforts adequate medical care for themselves and their dependents from doctors engaged in group-medical practice, to restrain doctors serving on its medical staff, to restrain other doctors in the District of Columbia in the pursuit of their callings, and to restrain the Washington hospitals in the operation of their business.

The defendants demurred to the indictment. Judge Proctor of the District Court of the District of Columbia decided in favor of the defendants, sustaining the demurrer. The government petitioned the Supreme Court of the United States for a writ of certiorari which, if granted, would permit appeal to the Supreme Court; this was denied. The rest of the article is devoted to a review of the legal questions raised by the demurrer, as submitted by both sides, and is a voluminous digest of the purposes and meaning of the language of the Sherman Act.

This is an important precedent which may have repercussions in future cases, because it seems to be established that medical societies, organized legally and with rules relating to membership or behavior of members that are not found to be illegal, may find that other organizations engaged in furnishing medical care may not meet the approval of the local medical society.

The tenth chapter is devoted to the "Background of the Wagner National Health Bill," by Harold Maslow, formerly staff member of the Committee on Research in Medical Economics. This bill is based on earlier experiences, studies, conferences and enactments relating to or brought about by socioeconomic conditions.

The Act passed in 1918 provided federal grants to state venereal-disease programs. Other bills for grants-in-aid followed, but many health problems received little legislative encouragement until the passing, in 1921, of the Sheppard-Towner Bill, which provided grants to states for infant and maternal hygiene. In 1934 President Roosevelt appointed a committee to draft a social security bill which provided for federal grants for public health and infant and maternal hygiene; these were amplified in 1939 under the social-security provisions of the Wagner Bill.

After the passage of the Social Security Act, the President appointed an Interdepartmental Committee to coordinate health and welfare activities. This committee in turn appointed the Technical Committee on Medical Care to continue studies of the 1934 committee. These committees submitted two reports in 1938,—"The Need for a National Health Program" and "A National Health Program,"—which were submitted to Congress and designed to interest the people in the extension of medical services according to a ten-year program, with the result that, in 1938, representatives of the professions, labor, farmers and civic bodies were invited and came to the National Health Conference.

Since that time there has been a tendency to endorse the propaganda of unmet health needs and focus public discussion on plans for meeting such deficiencies. The reports of these committees were presented to Congress with the result that the Wagner Bill was introduced. Extensive hearings on the bill were conducted with farmers, labor interests and some physicians in favor and the American Medical Association in opposition. In August, 1939, the subcommittee reported agreement with the general purposes and objectives of the bill, with recommendation for further study.

The provisions of the Wagner Bill, which is, in substance, a series of amendments to the Social Security Act, with some new features, are fully discussed. In this account there is abundant opportunity for the student to speculate on the questions which naturally arise when individuals engage in propaganda concerning complicated economic or sociological problems in which health plays a prominent part. Sympathy for human suffering and political exigency may be entwined perhaps unconsciously with the possibility of undue influence in one direction or

another by a mind swayed by emotion rather than logic. It is certainly true that when questions of relief from human suffering are to be considered, those people who are trained to deal with ill health are best qualified to solve many of these problems and should be recognized rather than those who see political advantage in large expenditure of public funds; hence it is reasonable to expect that in dealing with health matters, every opportunity for cooperation by the medical profession should be cordially encouraged. The Wagner Bill has been a source of controversy which might have been avoided if, in its earlier stages, cordial relations with the medical profession had been established.

The eleventh chapter deals with "Public Medical Services also under Title XIII of the National Health Bill," the author being David F. Cavers, professor of law, Duke University, who shows that the implications in the bill indicate that under its provisions there is the possibility of the enactment of compulsory health insurance in addition to uncontroversial projects. He goes on to show that since the depression the burdens imposed by illness and indigency have been too heavy for the support of taxpayers' hospitals, physicians and very many charitable agencies. In order to meet these conditions, the Emergency Relief Administration was devised, and in 1934, twenty-nine states were receiving assistance from this organization, but even so, the situation was not satisfactory, according to a report of the Committee on Medical Care of the American Public Welfare Association in 1938.

The twelfth chapter presents "Legislative Proposals for Compulsory Health Insurance," by Louis S. Reed, chief of the Medical Economics Section, Health Studies Division, Bureau of Research and Statistics, Social Security Board. In connection with studies of the desirability of legislative action, he submits the drafts of three state bills in addition to a model bill, composed by the American Association for Social Security, which was drawn in cooperation with leading authorities. The first had been drawn up in California by the Governor's Committee on Health Insurance; the second had been introduced in the New York Assembly; the third had been considered in the Wisconsin Assembly in 1937, a few changes having been made by Mr. Andrew Biemiller. Not one had been enacted up to the writing of this chapter. These four bills are designed to provide adequate medical care and spread the burden of illness costs, and all exclude from compulsory coverage the self-employed and two exclude farm and domestic service workers. All, except the California bill, limit compulsory coverage to manual workers and non-manual employees earning less than $3000 a year.

The fundamental principles here set forth are very much like those in old-age insurance, and questions arise as to the limits of health insurance to incomes, in so far as the medical service in the low-income groups may not equal that provided for the well-to-do and the complications incident to administration of these laws.

The thirteenth chapter, by I. S. Falk, L. S. Reed and B. S. Sanders, the last being chief of the District of Columbia Bar, covers the "Formulation of Disability Insurance." They show that because of the effects of the depression, the United States is following the trend in other nations toward social insurance which, in wider scope, will lessen the insecurity due to loss of earnings through unemployment, as already provided in certain provisions by the federal government and forty-seven states. In the Wagner Bill, under Title XIV, a proposal is submitted for a federal-state system of temporary disability insurance, and this, with proposed amendments in H. R. 6635, seems to be a pattern for the development of an amplified form of social insurance. The need for this seems indicated by the amount of dependency traceable to disabling illness and by the wage losses due to disabling illness, "as shown by opinions founded on fact finding studies indicating that thirty-five per cent to fifty per cent of poverty asking for relief is due to sickness." Statistics in this article are submitted in confirmation of these facts.

As the argument proceeds from explanation of the underlying causes and varieties of disabilities, all the complicating factors are discussed in extenso, and the varieties of relief indicated are defined in the conclusion reached that disability and invalidity insurance will necessitate a sharing of the costs by employers and employees and further that large expenditures by federal, state and local governments are warranted because the security now provided is inadequate.

The last chapter by Clarence Heer, professor of economics at the University of North Carolina, is devoted to a study of the formula for grants-in-aid and of the Wagner Bill, which is officially entitled the National Health Act of 1939. This is "primarily a grant-in-aid measure" with detailed specifications covering conditions under which the several states may, if so desired, receive funds from the federal government to assist them in specified health services under their own devised and administered plans. It provides an appropriation of $98,000,000 of federal money during the first year of operation, of which $89,000,000 will be paid to the states as grants-in-aid, with the understanding that such grants will depend on the states' raising matching funds. If state co-operation is forthcoming "it is estimated that some ten years hence, when the program reaches its maximum, federal grants for various public services, for medical care to the needy, and for the construction and maintenance of hospitals but excluding grants for state sickness-insurance claims, will reach a total of $425,000,000 per annum." With matching state appropriations, the sum will be $850,000,000 and will represent a net addition to the $571,000,000 of federal, state and local funds which, according to estimates, are now being spent on public-health services and hospital care in the United States.

Anyone interested in the published facts and conclusions which have appeared in the last decade pertaining to the sociological problems of health and to the laws designed to broaden the scope of measure dealing with them will find in these papers a résumé of facts and opinions which have a bearing on the changing attitude of the public toward medicine. There is, however, a rift to be bridged before the ethical principles of the profession will be generally interpreted and adopted by the public; this will be accomplished only when there shall have been brought about a more general appreciation of the devotion of the profession to human needs. Now that the legal fraternity has shown its interest in the accomplishments of medicine there should follow an enthusiastic endorsement of the aims and purposes of organized medicine.

Sclerosing Therapy: The injection treatment of hernia, hydrocele, varicose veins and hemorrhoids. Edited by Frank C. Yeomans. 337 pp. Baltimore: Williams & Wilkins Co., 1939. $6.00.

In this book, treatment by the injection of sclerosing fluids into hernias, hydroceles, varicose veins and hemorrhoids is considered. The last two topics, presented by Shelley and Yeomans respectively, are clear, well-illustrated and conservative expositions which can be read with profit by those interested.

As Hoch points out in the second article, the surgical

treatment of hydrocele is accompanied by a rather high incidence of wound complications. Injection treatment, which is well described, should therefore have much to offer, but one is disappointed to find no statistical analysis of the results or complications of the method.

The same criticism can be made, to a considerable extent, of the first and longest article in the book. In it, Bratrud carefully reviews the subject of the injection treatment of hernia from the point of view of ten years' experience as director of the clinic for ambulant treatment of hernia of the University of Minnesota Medical School. Indications, contraindications and technics are well described and illustrated, but in the chapter on results one finds only very scanty data on the duration of cure. The most careful, and discouraging, study of end results that has thus far appeared, that of Burdick and Coley from the Hospital for the Ruptured and Crippled of New York City, is dismissed in a sentence.

It seems to the reviewer that the author of this section, in common with all protagonists of the injection method of treating hernia, bases his work on the false assumption that scar tissue will not stretch. If such were the case infected abdominal wounds healing by secondary intention should never herniate, but unfortunately they do with considerable frequency. However, for those few individuals who refuse operation or for whom operation is contraindicated, the method is worthy of trial.

For the surgeon who is called on to employ sclerosing therapy the book can be highly recommended.

The Physiological Basis of Medical Practice: A University of Toronto text in applied physiology. Charles H. Best and Norman B. Taylor. Second edition. 1872 pp. Baltimore: Williams & Wilkins Co., 1939. $10.00.

The first edition of this book was issued in 1937 and at once became the standard and most popular book of its day, linking together the preclinical subject of physiology and that of medical practice. A large book, full of material, it has become a bible of the junior clinician, for it bridges his medical-school work with actual contact with patients in the clinic or hospital. Accurately written, extensively documented and widely supplied with charts and diagrams, it is not surprising that this book has been reprinted four times before a second edition was called for two years after the first was issued.

In this new edition, the material has been carefully revised, and a new section on the special senses added. In order to save space, which is an important consideration in a book of its size, the titles of papers have been omitted from references, unless necessary for the identification of the paper. There is an extensive bibliography by chapters at the end of the book, listing not only the important papers on the subject but also monographs and reviews. In addition, the book is thoroughly indexed. As a reference book, this volume is outstanding.

Health in Handcuffs. John A. Kingsbury. 210 pp. New York: Modern Age Books, Inc., 1939. 75c.

This book, written by the former executive officer of the Milbank Fund, is published for the purpose of showing that health administration and the resources of scientific medicine are not operating to capacity because of several inhibiting factors. After an appreciative tribute to the medical profession and other agencies included in dealing with the problems of illness and the economic complications incident thereto, the author explains the complexities involved in the adjustment of the resources of this nation to the prevailing sociologic conditions and expresses his belief that health insurance in one form or another will play an important part in dealing with them. Endorsement of the principle underlying group practice and adequate hospitalization of a larger proportion of the population are among other propositions advanced.

The major trend of the belief of Mr. Kingsbury, however, is in the advisability of the passage of the health program as set forth in the Wagner Act and to this end a large proportion of his arguments is directed. This has brought him into conflict with the attitude of the American Medical Association, which he assails in the spirit of a crusader.

The book is well written and contains much information covering the propositions of federal bureaus and departments with respect to the health program defined in the bill before Congress.

Bergey's Manual of Determinative Bacteriology: A key for the identification of organisms of the class schizomycetes. David H. Bergey, Robert S. Breed, E. G. D. Murray and A. Parker Hitchens. Fifth edition. 1032 pp. Baltimore: Williams & Wilkins Co., 1939. $10.00.

The practicing bacteriologist cannot but feel that he owes a debt of gratitude to those of his colleagues who have been willing to keep this now well-established manual up to date. To review it properly would require a detailed study which the present reviewer has not been able to give. In the past he has found occasional errors in this book or, let us say, points in which his opinion differed from that of the original author. But these were never important and did not diminish the great importance of the manual as a reference book for all bacteriological laboratories.

The task of the present authors has been rendered particularly difficult by the changes in bacterial classification which have resulted from the newer knowledge of dissociation. They are aware of this, however, and the reviewer agrees with them that none of this work has necessitated fundamental changes in a systematic classification of this kind. The bacteriologist who, like the reviewer, is engaged in the study of purely pathogenic bacteria is quite incompetent to judge the book as a whole. But in those sections with which he is familiar he finds this new edition as valuable as he has found preceding ones. The nomenclature is a bit confusing to the "old hand," who has difficulty in recognizing some of his old friends under new names. And he is apt to wonder why such first cousins — almost twins — as the gonococcus and meningococcus which, unless the source is known, are not easy to tell apart, are separated in different families seventeen pages apart. But these and similar examples are all points in which legitimate differences of opinion are possible and do not detract from the great value of this book which performs a difficult and necessary service.

Lane Medical Lectures: Viruses and Virus Diseases. Thomas M. Rivers. 133 pp. Stanford University, California: Stanford University Press, 1939. $2.50.

Dr. Rivers, director of the Hospital of the Rockefeller Institute for Medical Research, has had published in book form the Lane Medical Lectures, given by him in 1939. The subject is highly technical but of great interest to physicians who are keeping up with progress in bacteriology. Dr. Rivers discusses lymphocytic choriomeningitis, the pathology of virus diseases, immunologic and serologic phenomena of virus diseases, and their treatment and prevention. The work summarizes the latest advances in this field of medicine and, as such, is an invaluable addition to medical literature.